Lutonix™ Drug Coated Balloon Device for the Treatment of Femoropopliteal Artery Disease

June 12, 2014

CR Bard Corporation

Lutonix, wholly owned subsidiary of CR Bard Inc.

FDA Circulatory System Devices Panel

Introduction to Lutonix Drug Coated Balloon (DCB)

John DeFord, PhD
Senior Vice President
Science, Technology and Clinical Affairs
C.R. Bard, Inc.

Lutonix DCB Combines a Proven PTA Device with a Proven Drug Paclitaxel

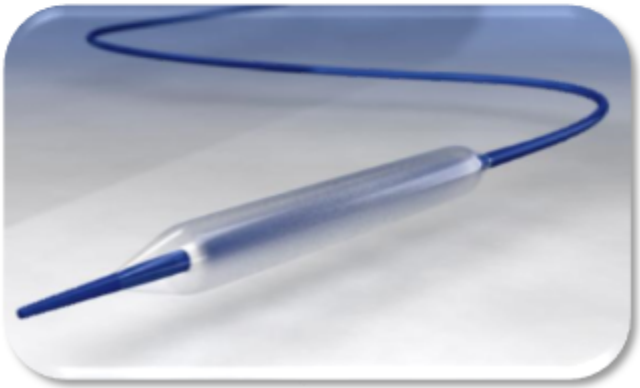
Percutaneous Transluminal Angioplasty (PTA)

- Approved for endovascular use since 1970s

Paclitaxel

- Approved for arterial local drug delivery since 2004 (i.e. Taxus, Zilver PTX)
- Approved as a chemotherapy agent since 1992

Lutonix DCB

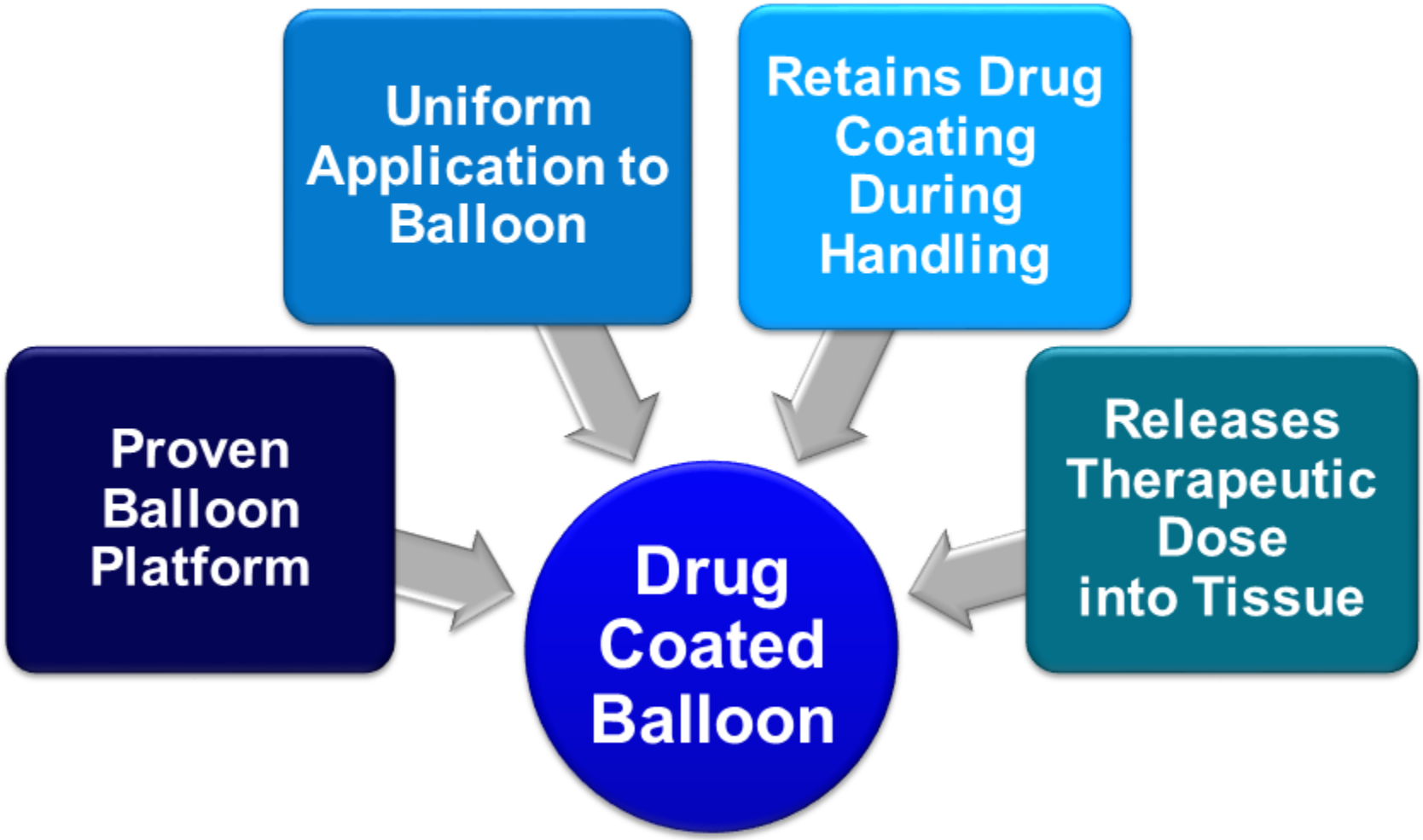


Paclitaxel is a Well-Characterized Anti-Restenotic Agent

- Safe and effective anti-restenotic agent[1,2]
- Binds cellular microtubules[3]
- Inhibits cell division, migration, and secretion[4]
- Local vascular application inhibits smooth muscle cell proliferation and neointimal hyperplasia[5]

[1]TAXUS™ Express Paclitaxel-Eluting Coronary Stent System, PMA approved 03/2004
[2]Zilver® PTX Drug-Eluting Peripheral Stent, PMA approval 11/2012
[3]Schiff, 1979
[4]Waksman, 2002
[5]Sollott, 1995; Axel, 1997

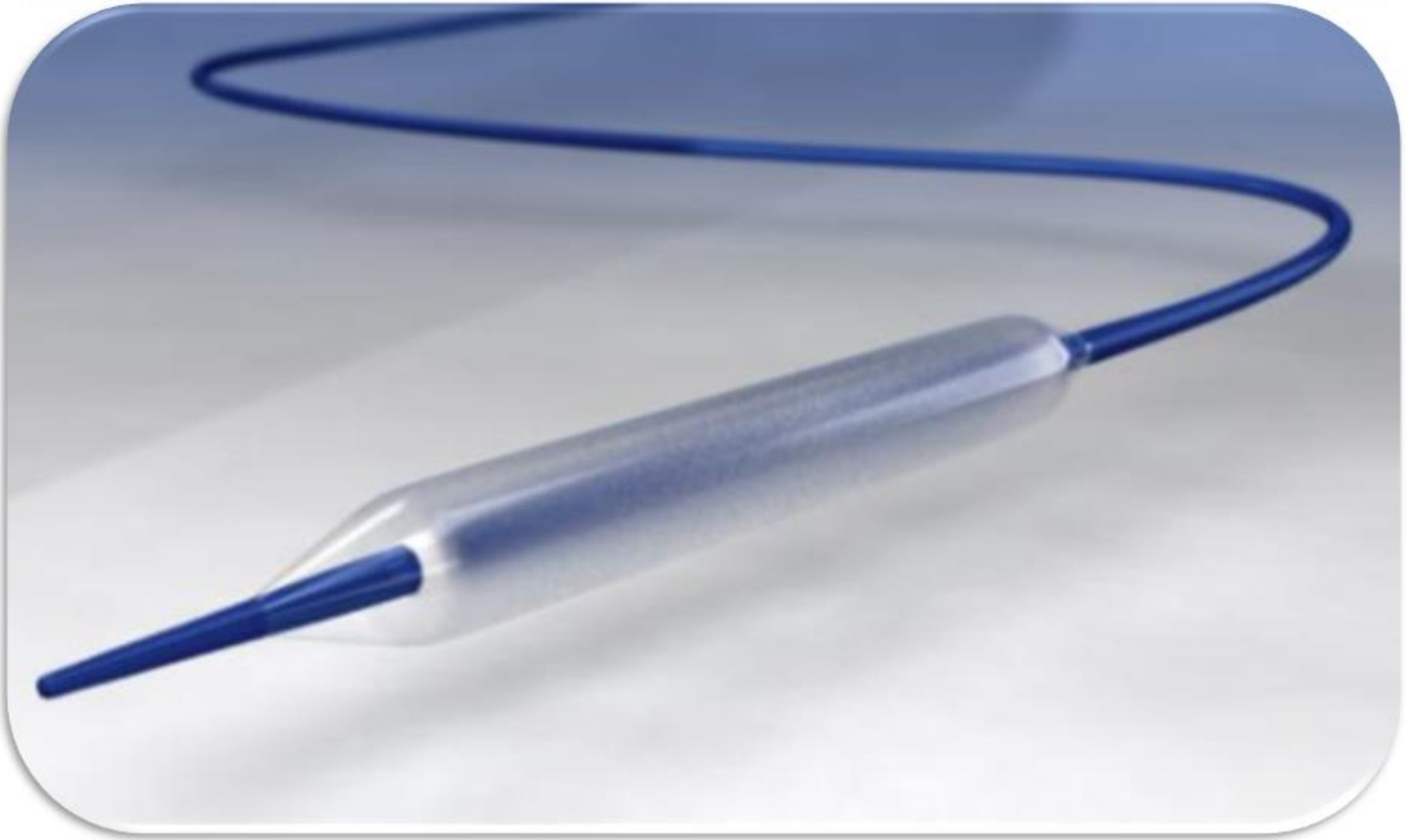
Design Elements of Drug Coated Balloons



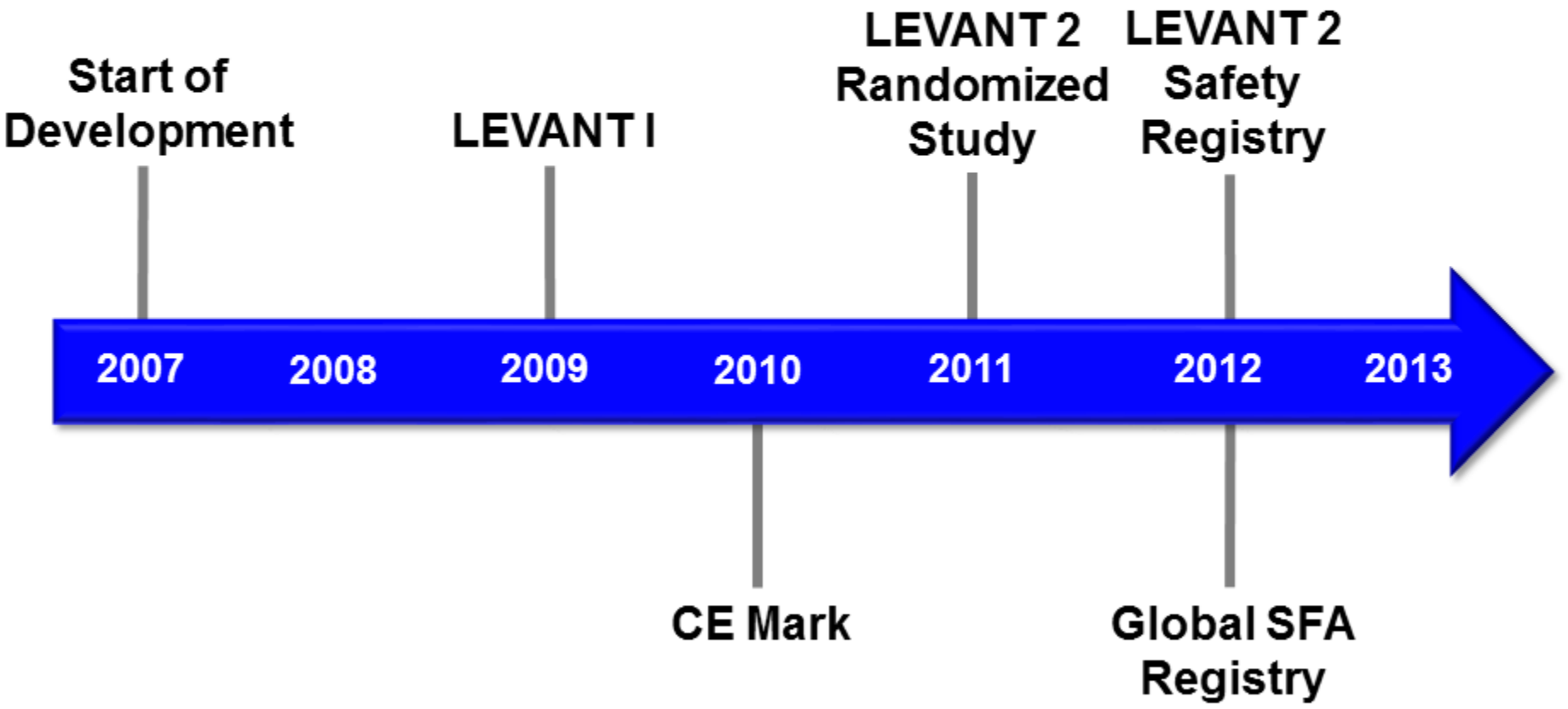
Extensive Pre-Clinical Research to Develop Coating Formulation

- 250 formulations studied
- Pre-clinical testing demonstrated 2 μg/mm^2 paclitaxel dose with excipients achieved therapeutic drug levels
- Excipient includes polysorbate and sorbitol

Lutonix DCB is Similar to Standard Angioplasty



Extensive Clinical Development and Patient Experience



Extensive SFA Clinical Experience with Lutonix DCB

LEVANT I	LEVANT 2	Safety Registry	Global SFA Registry	Total Patients
Randomized N=49	Roll-in N=56 Randomized N=316	N=657	N>500*	N>1,500

- Lutonix DCB used to date: >10,000
- Outside the US DCB used per year: >80,000

*Enrollment ongoing

LEVANT 2 Met Both Primary Endpoints

- Designed to evaluate improved durability of angioplasty with addition of drug coating
- Efficacy: primary patency superiority
  - Lutonix DCB 65.2% compared to 52.6% in Standard PTA ($p = 0.015$)
- Safety: composite endpoint non-inferiority
  - Lutonix DCB 83.9% compared to 79.0% in Standard PTA ($p=0.005$)

Proposed Indication

- **The Lutonix® 035 Drug Coated Balloon** PTA Catheter is indicated for improving luminal diameter for the treatment of obstructive **de novo or non-stented restenotic** lesions **(≤ 15 cm in length)** in native femoropopliteal arteries **having reference vessel diameters of 4 mm to 6 mm.**

Agenda

Unmet Need and Clinical Trial Design	**Kenneth Rosenfield, MD** Section Head for Vascular Medicine and Intervention Study Co-PI Massachusetts General Hospital
Efficacy	**Michael R. Jaff, DO** Medical Director, VasCore Chair, Institute for Heart, Vascular and Stroke Care Massachusetts General Hospital
Safety	**Gary Ansel, MD** System Medical Chief, Vascular Services Ohio Health/Riverside Methodist Hospital
Interactions	**Chris Mullin, MS** Statistican NASMA
Post-Approval	**John DeFord, PhD** Senior Vice President Science, Technology and Clinical Affairs C.R. Bard
Benefit-Risk	**Jihad Mustapha, MD** Director of Cardiovascular Catheterization Laboratories Clinical Assistant Professor of Medicine Michigan State University

Additional Expert Responder

Marguerite Brackley, MD	CEC Member Independent Medical Reviewer
Richard Chiacchierini, PhD	Statistician
Dierk Scheinert, MD	Professor of Medicine, Chairman Center for Vascular Medicine Park Hospital Leipzig and Heart Center University of Leipzig
Renu Virmani, MD	Cardiovascular Pathology CVPath Institute

Peripheral Artery Disease
Unmet Need

Kenneth Rosenfield, MD

Section Head for Vascular Medicine and Intervention

Massachusetts General Hospital

Peripheral Artery Disease (PAD)

- Plaque build-up in non-coronary blood vessels
- Narrows arteries
- Compromises blood flow to lower extremities
- Causes leg pain (intermittent claudication)
- Disability
- Amputation

Prevalence of PAD

- PAD is common, present in up to 8 million patients in the US[1]
- More common in association with diabetes[1]
- Prevalence: 20% in those >70 years of age[2]
- Mortality due to cardiovascular cause – 6x greater in patients with PAD vs. those without PAD[3]

[1] American Heart Association, 2012 [2] Kannel, 1996, Hirsch, 2006 [3] Criqui, 1992

PAD: Substantial Effect on Patient Quality of Life[1]

- Symptomatic PAD – not just a minor discomfort; often has major impact on patients
  - Reduced quality of life
  - Inability to perform activities of daily living
- May progress to critical limb ischemia: pain at rest, ulcers, gangrene
  - ~15% of diabetic population, with increased risk of amputation

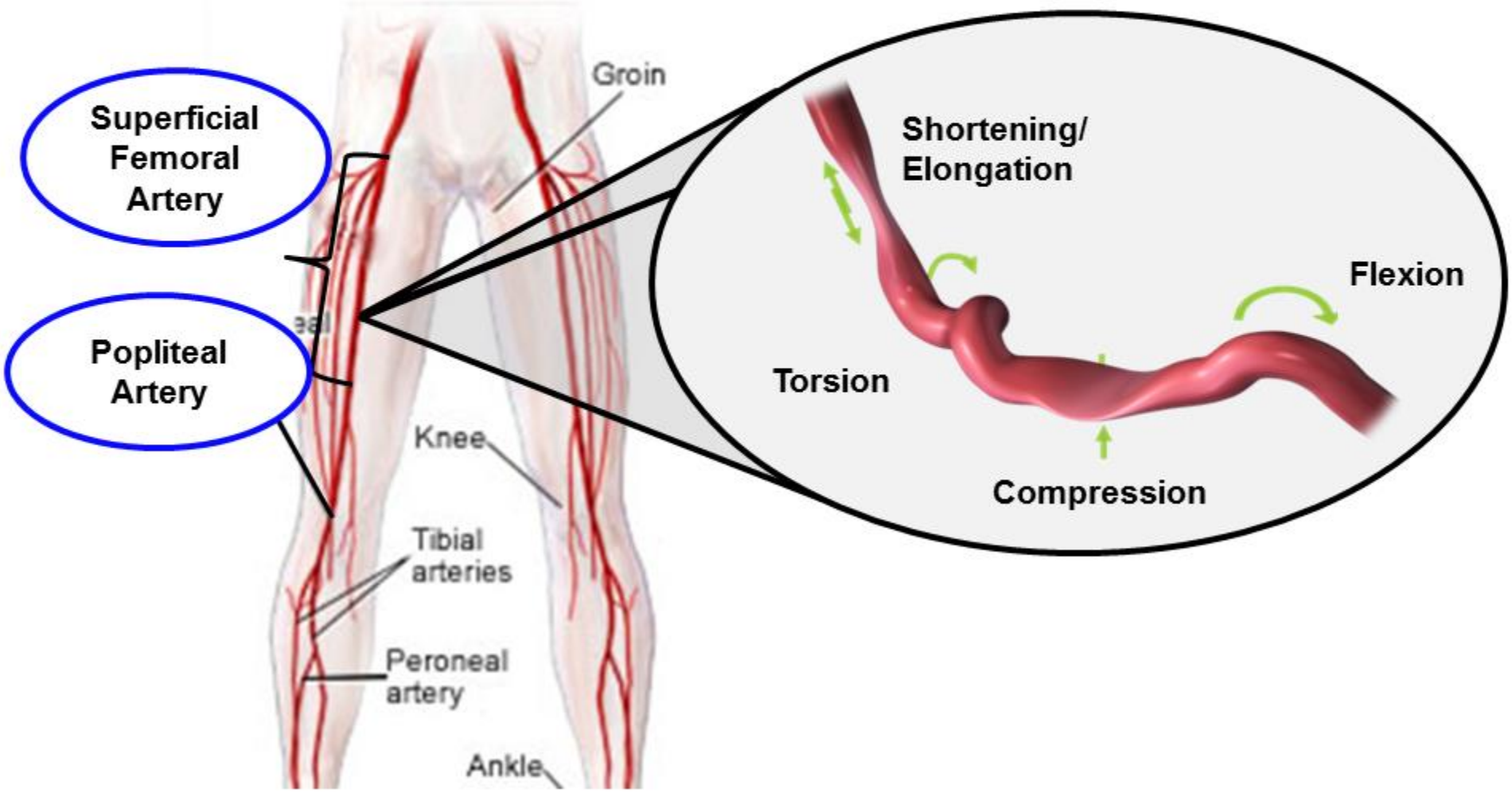
[1] Hirsch, 2006; Reiber, 2002; Most, 1983

CV Event Rates in the PAD Cohort of the REACH Registry at 1 Year[1]

Common Co-morbidities	REACH (PAD Cohort) (n=8581)
Obesity	23.8%
Hypertension	81.0%
Diabetes	44.2%
1 Year CV Event	
All-cause mortality	3.76% (3.27 - 4.25)
CV death	2.51% (2.10 - 2.92)
Nonfatal MI	1.29% (1.01 - 1.58)
Nonfatal stroke	1.92% (1.56 - 2.27)
CV death, MI, or stroke (MACE)	5.35% (4.77 - 5.97)
CV Hospitalization	21.14% (20.2 - 22.1)

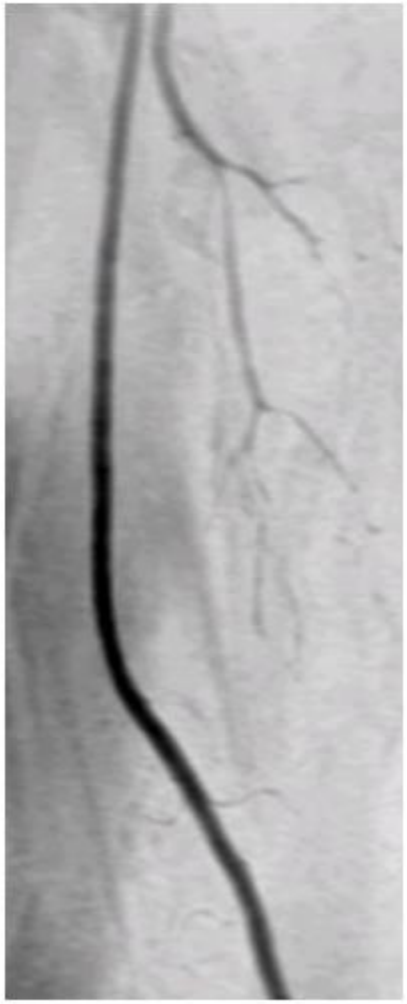
[1]Bhatt, 2006; Steg PG., 2007

Femoropopliteal Artery Most Commonly Diseased Artery in Peripheral Circulation

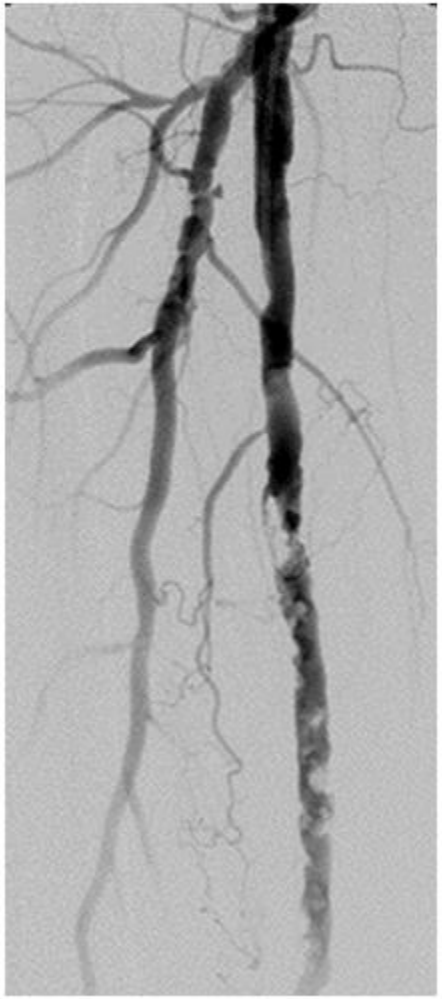


Levy, 2002; Klein, 2009

Typical Femoropopliteal Angiograms



Patent



Diseased

Current Treatment Options Available[1]

Pharmacotherapy Diet / Exercise	Endovascular Procedure	Surgical Bypass

Limited by

- Medication intolerance (30%)
- Lack of medication efficacy (50%)
- Poor patient compliance

Lower rate of complications

Limited by

- Increased morbidity/mortality

[1] Hiatt, 2008; Dawson, 2000; Parmenter, 2011

Primary Goal of Therapy: Patency

- Relief of the obstructing arterial blockage
- Typical primary endpoint used in PTA trials
  - Meaningful and clinically relevant
- Patency is an appropriate, concrete, quantitative measure
- Patency ends when there is significant obstruction, typically associated with recurrence of patient symptoms

Widespread Use of Primary Patency as Efficacy Endpoint

- VIVA OPG[1]
- FDA SFA IDE trials used primary patency as primary endpoint
  - RESILIENT[2]
  - ZILVER PTX[3]
  - DURABILITY[4]
  - COMPLETE SE[5]
  - STROLL[6]
  - SUPERB[7]

[1]Rocha-Singh, 2007 [2]Laird, 2010 [3]Dake, 2011 [4]Bosiers, 2009 [5]Laird, 2014 [6]NCT00739102 [7]NCT00933270

PAD Treatment Options and Patency

- PTA cornerstone of endovascular therapy for last half-century
  - First line, standard of care[1]
  - One-year patency without reintervention as low as ~33%[2] (lesions 4-15 cm)
- Introduction of stents
  - One-year bare metal or drug eluting stent patency rates ~63-81%[3]

[1]Rooke, 2011 [2]Rocha-Singh, 2007
[3]Laird, 2010; Schillinger, 2006; Krankenberg, 2007; Dake, 2011

Limitations to Stenting in SFA and Popliteal[1]

- May lead to fracture and vessel injury
- Ongoing stimulus for restenosis
- May jail collaterals
- May limit future surgical options
- Restenosis very challenging to treat
- Not suitable for “no stent zones”
- Requires antiplatelet or dual antiplatelet therapy for drug eluting stents (DES)

[1] Levy, 2002; Scheinert 2005; Klein, 2009

Conclusion

- Significant clinical need remains for a device
  - Achieves more durable patency
  - Does not require a permanent implant
- Non-implantable endovascular therapies provide clinicians with
  - First line of treatment in SFA and popliteal
  - Leaves future treatment options open
  - Better treat a broader patient population

Study Design

Randomized Clinical Trial Design

Design	Prospective, Randomized, Single-blind Lutonix DCB vs Standard PTA
Randomization	2:1
Sites	42 US 12 EU (Germany, Belgium, Austria)
Follow-up	**Clinical:** 6, 12 & 24 months **Duplex Ultrasound (DUS):** 0-30 days, 6, 12 & 24 months **Telephone:** 1, 36, 48 & 60 months

Unique Design Considerations to Minimize Confounding

Effect of drug	→	Strive to minimize stenting
Remove bias during clinical assessment for re-intervention	→	Blinding strategy
Assess durability of treatment vs acute results	→	Bailout stenting not counted as a failure

Unique Design Considerations to Minimize Confounding

Effect of drug	→	**Strive to minimize stenting**
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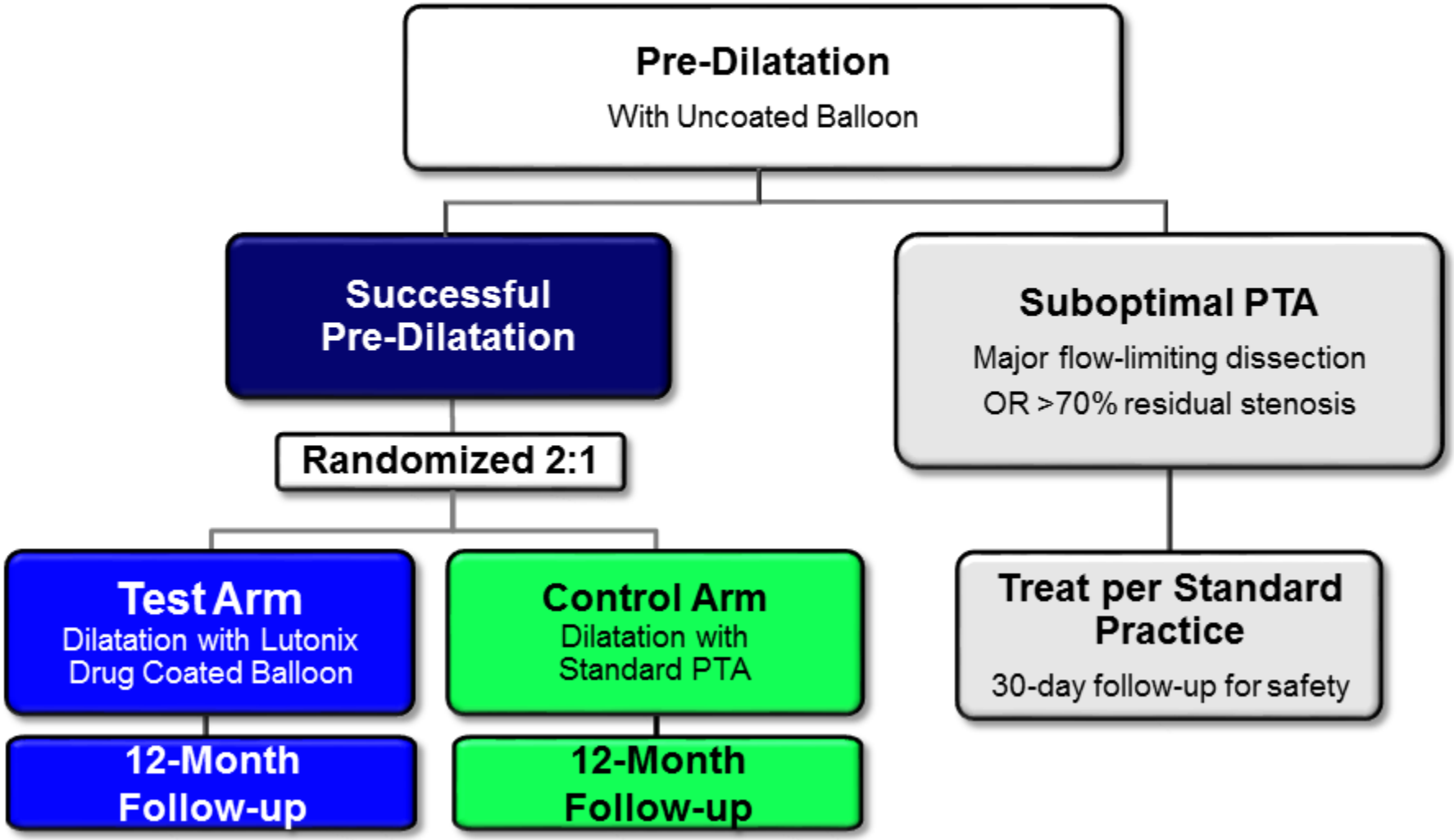
LEVANT 2 Study Flow



Unique Design Considerations to Minimize Confounding

Effect of drug	→	Strive to minimize stenting
Remove bias during clinical assessment for re-intervention	→	**Blinding strategy**
Assess durability of treatment vs acute results	→	Bailout stenting not counted as a failure

Extensive Blinding Steps Taken to Reduce Bias

Blinded

Randomization	30 days	6 months	12 months
• Patient • Core Lab	• Patient • Core Labs • DUS Tech • Evaluating Physician	• Patient • Core Labs • DUS Tech • Evaluating Physician	• Patient • Core Labs • DUS Tech • Evaluating Physician

Not Blinded

- Treating Physician

Unique Design Considerations to Minimize Confounding

Effect of drug	→	Strive to minimize stenting
Remove bias during clinical assessment for re-intervention	→	Blinding strategy
Assess durability of treatment vs acute results	**→**	**Bailout stenting not counted as a failure*[1]**

*40-50% bailout stent rate

[1]Laird, 2010 (RESILIENT); Dake, 2011 (ZILVER PTX)

Key Inclusion Criteria

- Clinical Criteria
  - Male or non-pregnant female
  - ≥ 18 years old
  - Rutherford Class 2 – 4
- Angiographic Criteria
  - ≥ 70% diameter stenosis
  - Length ≤ 15 cm
  - Diameter 4 – 6 mm

Key Exclusion Criteria

- Hemorrhagic stroke ≤ 3 months
- Chronic kidney disease (GFR <30 ml/dl)
- Life expectancy <5 years
- Unable to take study medications
- Prior vascular surgery of the index limb

Study Oversight

- Clinical Events Committee (CEC)
  - Blinded
  - Experts in vascular intervention
  - Adjudicated all events – determined seriousness and relatedness
- Data Monitoring Committee (DMC)
  - Experts in peripheral vascular disease, cardiovascular medicine and biostatistics
- Core Lab
  - Blinded
  - Duplex Ultrasound: VasCore
  - Angiography: SynvaCor

Efficacy Endpoint: Primary Patency at 12 Months

- Primary patency of the target lesion defined as both
  - Absence of core lab adjudicated target lesion binary restenosis

  AND
  - Freedom from CEC adjudicated target lesion revascularization (TLR)

Composite Safety Endpoint at 12 Months

- Freedom from all-cause peri-operative death

AND

- Freedom at 12 months from
  - Index-limb amputation
  - Index-limb re-intervention
  - Index-limb related death

Key Secondary Endpoints

- Target lesion revascularization (TLR)
- Target vessel revascularization (TVR)
- Rutherford Classification
- Walking Impairment Questionnaire
- Quality of life surveys (SF-36, EQ-5D)
- Death
- Amputation
- Limb re-interventions

Sample Size

- Powered for both primary efficacy and safety endpoints
  - ≥ 90% power
  - Sample size was 476 patients
- Sample size assumed 15% loss of patients
  - Study exits
  - Missing imaging data

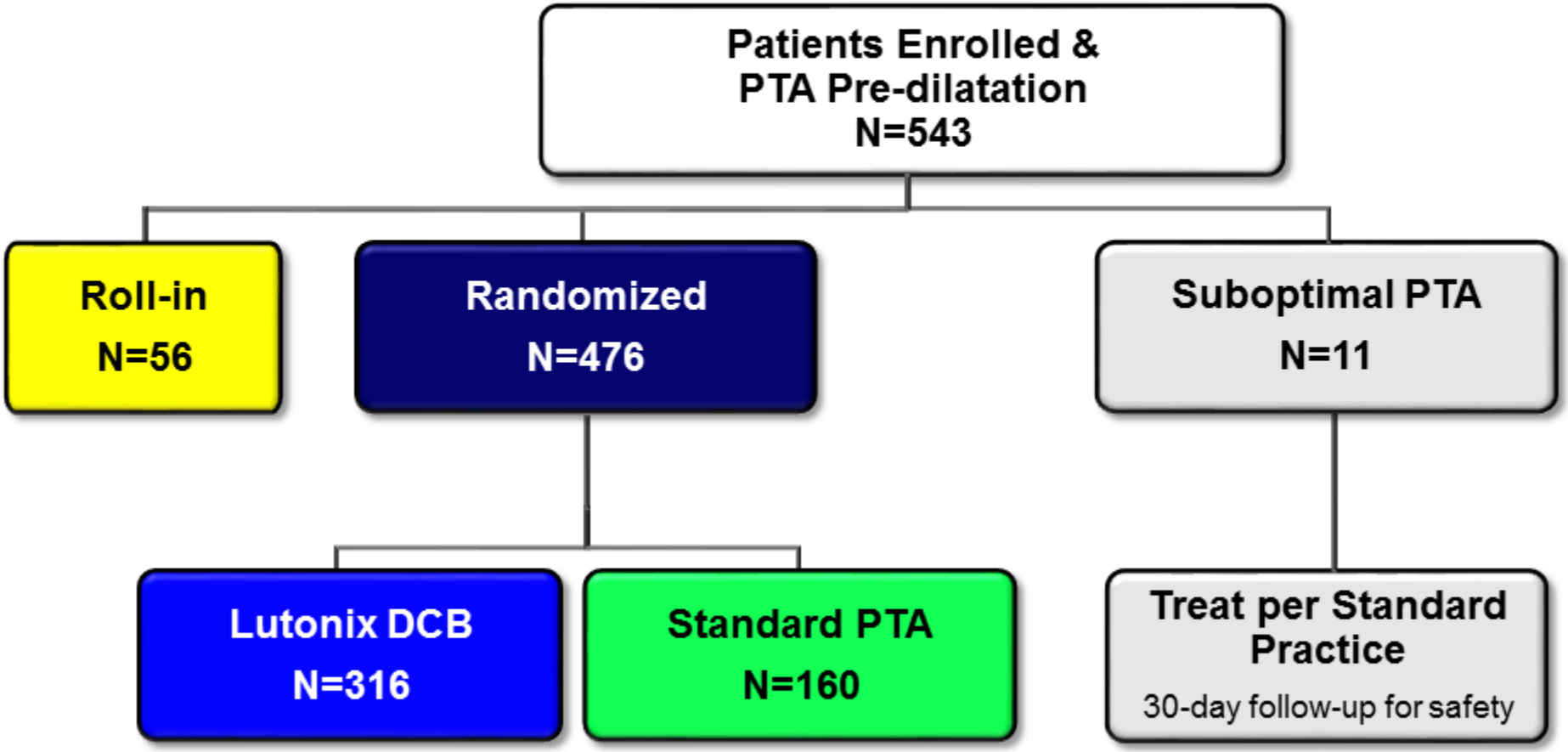
Poolability[1]

- Same protocol at all sites
- Block randomization within study sites
- Data gathering with same instruments
- Same CEC and core laboratories adjudicating

[1]Meinert, 1986

Baseline Patient Characteristics and Procedural Data

Patient Enrollment



Intent-to-Treat = As-Treated

- Intent-to-treat (ITT): All randomized subjects according to their assigned treatment, and evaluable at 12 months
- As-treated (AT): All randomized subjects according to the treatment received

- ITT = AT
  - All subjects in LEVANT 2 received assigned treatment

Baseline Demographics: Randomized Groups were Well Matched

	Lutonix DCB N=316	Standard PTA N=160	P-value
Age, mean ± SD	67.8 ± 10.0	69.0 ± 9.0	0.207
Male, n (%)	193 (61%)	107 (67%)	0.216
BMI ≥ 30 kg/m^2, n (%)	110 (35%)	49 (31%)	0.360
Current Smoker, n (%)	111 (35%)	54 (34%)	0.548
Diabetes, n (%)	137 (43%)	67 (42%)	0.758
Dyslipidemia, n (%)	283 (90%)	138 (86%)	0.286
Hypertension, n (%)	282 (89%)	140 (88%)	0.572
Coronary Artery Disease, n (%)	157 (50%)	77 (48%)	0.748

Rutherford and Ankle-Brachial Index Similar Results Between Arms

	Lutonix DCB N=316	Standard PTA N=160	P-value
Rutherford Classification, n (%)			0.521
2	93 (29%)	55 (34%)	
3	198 (63%)	92 (58%)	
4	25 (8%)	13 (8%)	
Ankle Brachial Index (ABI), mean ± SD			
Target Limb	0.74 ± 0.20	0.73 ± 0.18	0.467

Core Lab Determined Lesion Characteristics

	Lutonix DCB N=316	Standard PTA N=160	P-value
Total Lesion Length (mm)	62.7 ± 41.4	63.2 ± 40.4	0.900
Treated Length (mm)	107.9 ± 47.0	107.9 ± 49.4	0.988
Calcification	187 (59%)	93 (58%)	0.826
Severe	33 (10%)	13 (8%)	0.419
Total Occlusion	65 (21%)	35 (22%)	0.741

Procedure Characteristics

	Lutonix DCB N=316	Standard PTA N=160	P-value
Dissection, Grade C After Randomized Treatment, n (%)	8 (2.5%)	12 (7.5%)	0.011
Bailout Stenting, n (%)	8 (2.5%)	11 (6.9%)	0.022
Number of Balloons, mean (SD)	1.37 ± 0.50	1.13 ± 0.35	<0.001
Inflation Time (sec), mean (SD) (# of Balloons)	151.2 ± 78.1 (n=432)	173.6 ± 109.6 (n=180)	0.004
Inflation Pressure (atm), mean (SD) (# of Balloons)	7.8 ± 2.0 (n=432)	8.4 ± 2.6 (n=180)	0.002

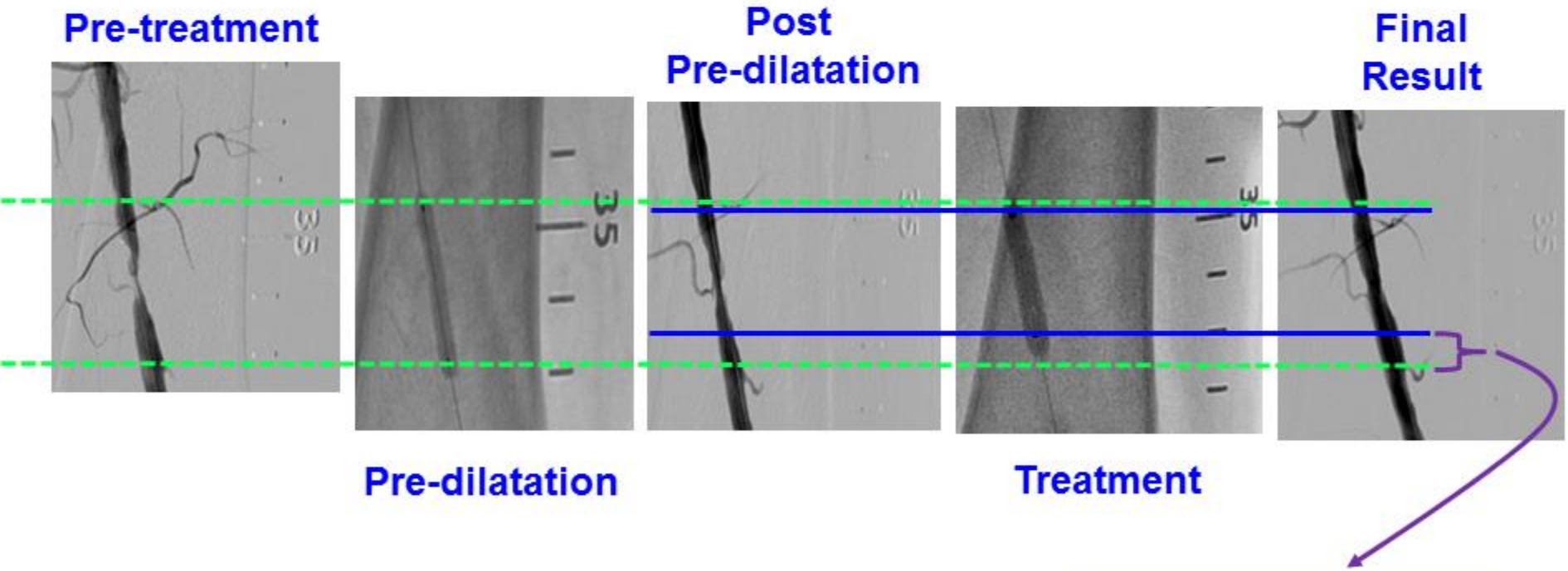
Procedure Characteristics

	Lutonix DCB N=316	Standard PTA N=160	P-value
Procedure Duration (min) mean, (SD)	57.6 ± 29.8	56.6 ± 29.2	0.741
Final % Diameter Stenosis, mean (SD)	20.9 ± 9.8	21.0 ± 10.2	0.914
Procedural Success (%)	88.9%	86.8%	0.497
Device Success, % (# of balloons)	99.5% (430/432)	100% (180/180)	0.361
Geographic Miss (%)	7.6%	21.9%	<0.001

Geographic Miss

- Any inflation, pre- or post-dilatation, in an area of the vessel not completely covered by the DCB or standard PTA balloon
  - DCB arm: not delivering drug to entire dilated segment = geographic miss
  - PTA arm: reinflating a balloon in an adequately treated segment is not best clinical practice

Geographic Miss



Geographic Miss

- Drug delivery not relevant for PTA
- Blinded core lab did not consider treatment group during assessment
- Treating physician not blinded, not concerned with delivering drug in PTA arm
- Procedural outcomes same for DCB and PTA
- Procedural outcomes same for geographic miss and non-geographic miss

Efficacy

Michael R. Jaff, DO
VasCore
Vascular Ultrasound Core Laboratory
Mass General Hospital

Efficacy Topics

- Use of duplex ultrasound (DUS) to assess primary patency
- Primary efficacy endpoint
- Supportive analyses
  - Subgroup results
  - Per Protocol
- Secondary endpoints

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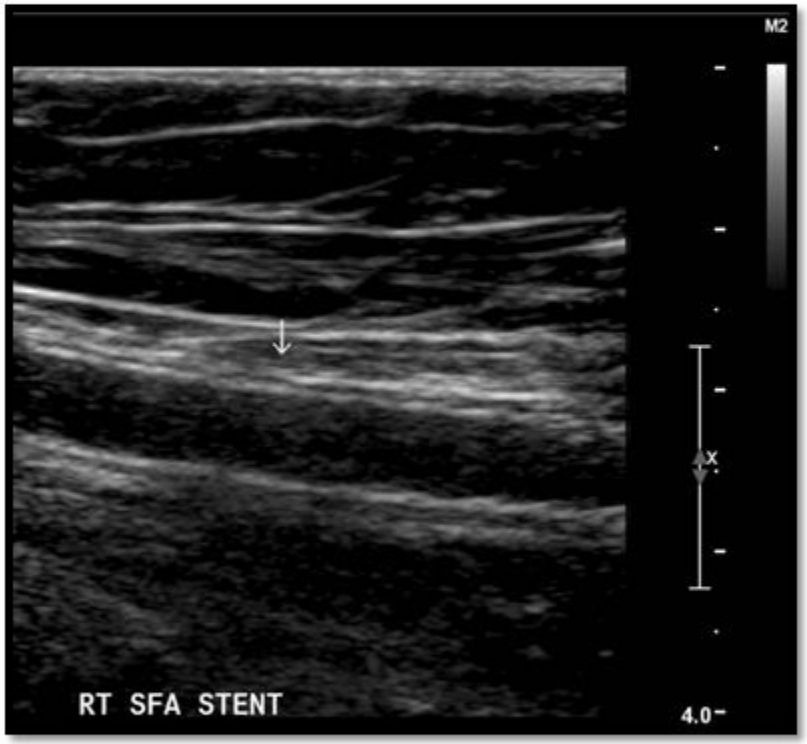
Primary Efficacy Endpoint

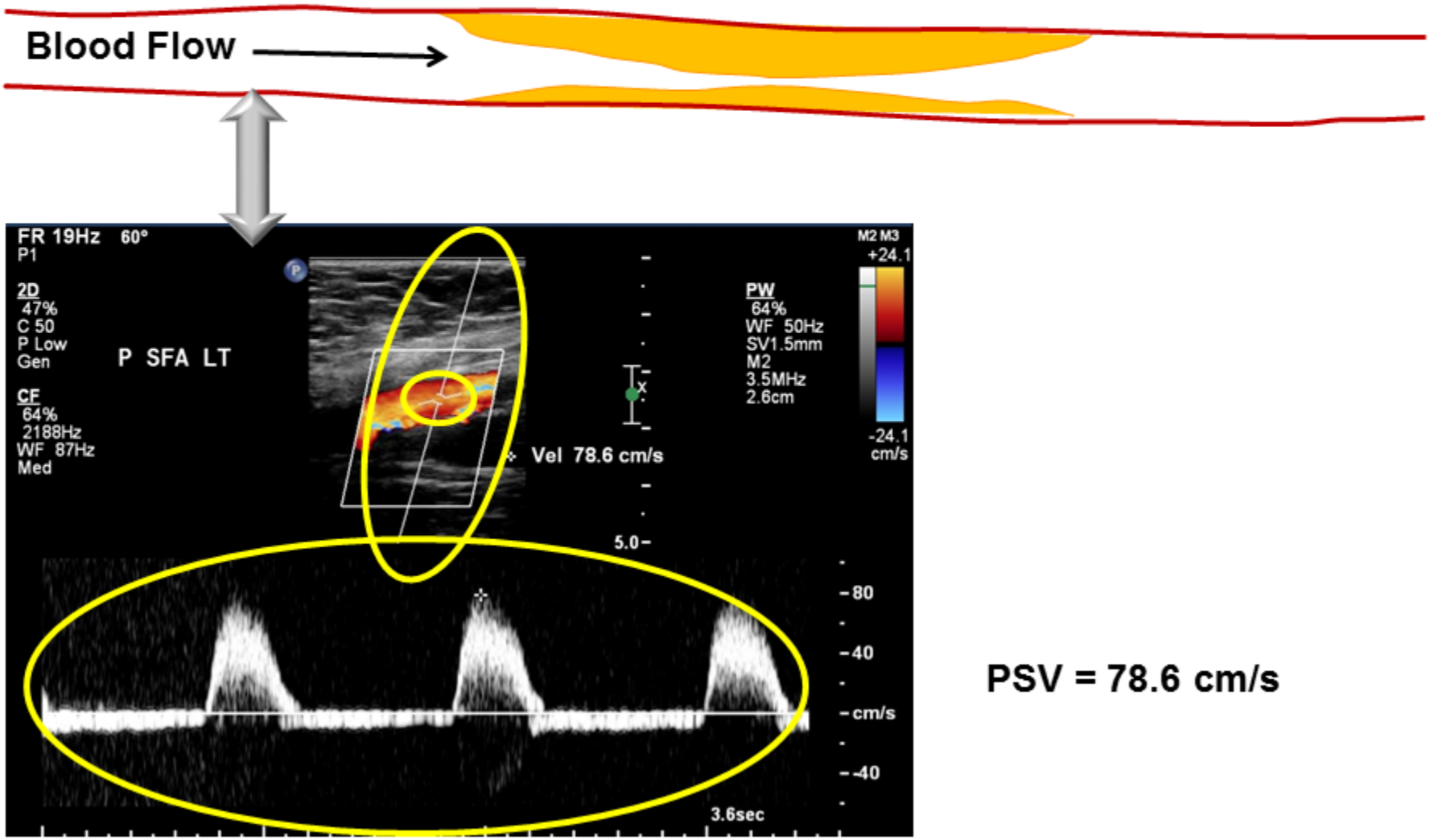
- Primary patency at 12 months, defined as freedom from
  - Binary restenosis
  - TLR
- Superiority
- Two sided, alpha = 0.05

Example of Normal Vessel



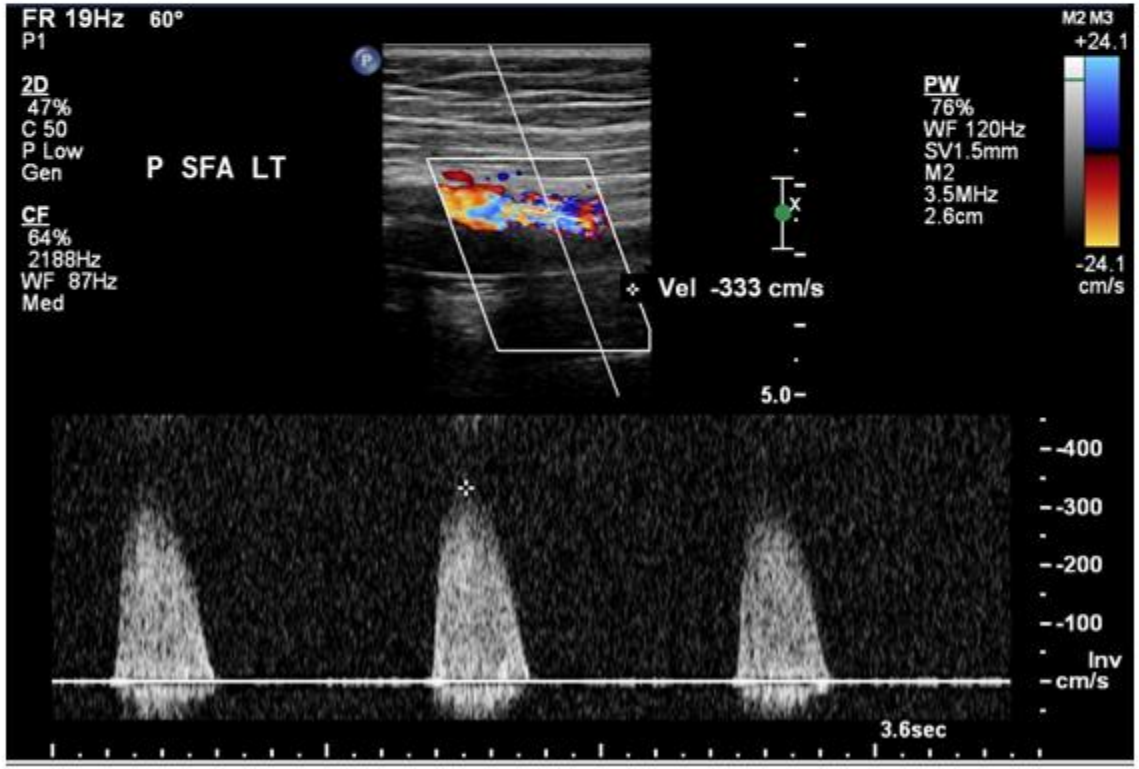
Blood Flow →

Duplex Image: Normal Proximal Artery



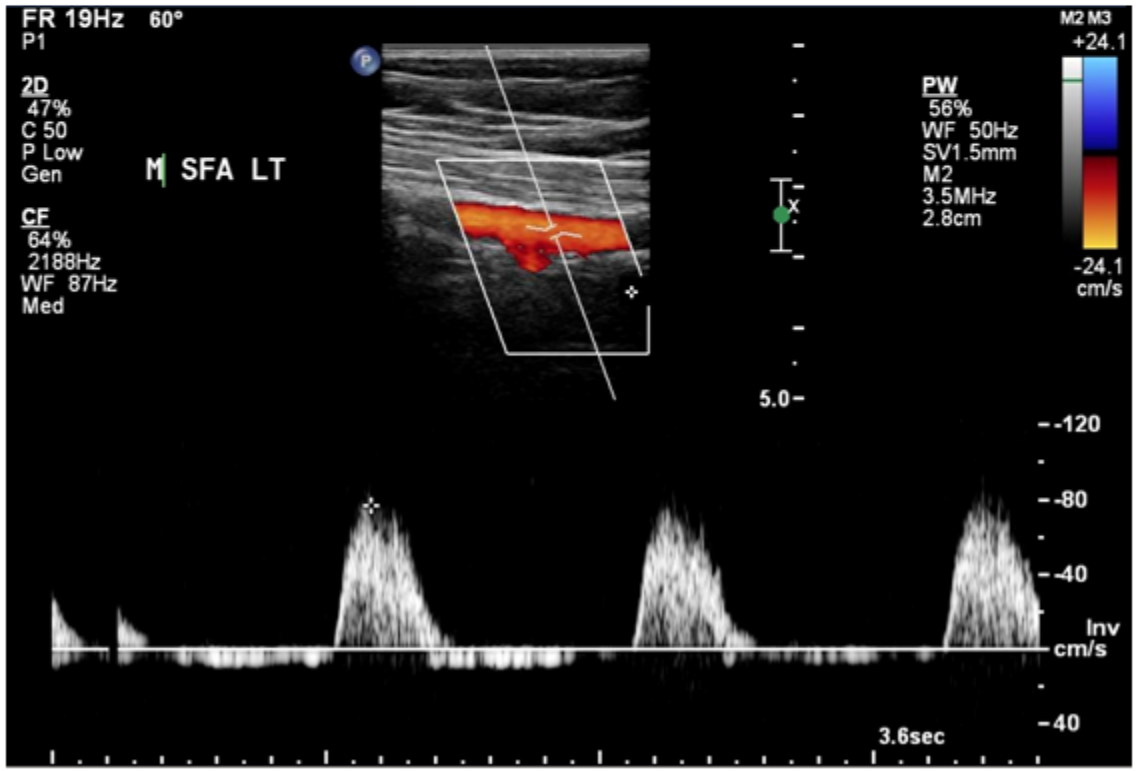
PSV = 78.6 cm/s

Duplex Image: Stenosis In Artery



PSV = 333 cm/s

Duplex Image: Distal to Stenosis



PSVR = 333/ 78.6 cm/s
= 4.3

Primary Patency via DUS

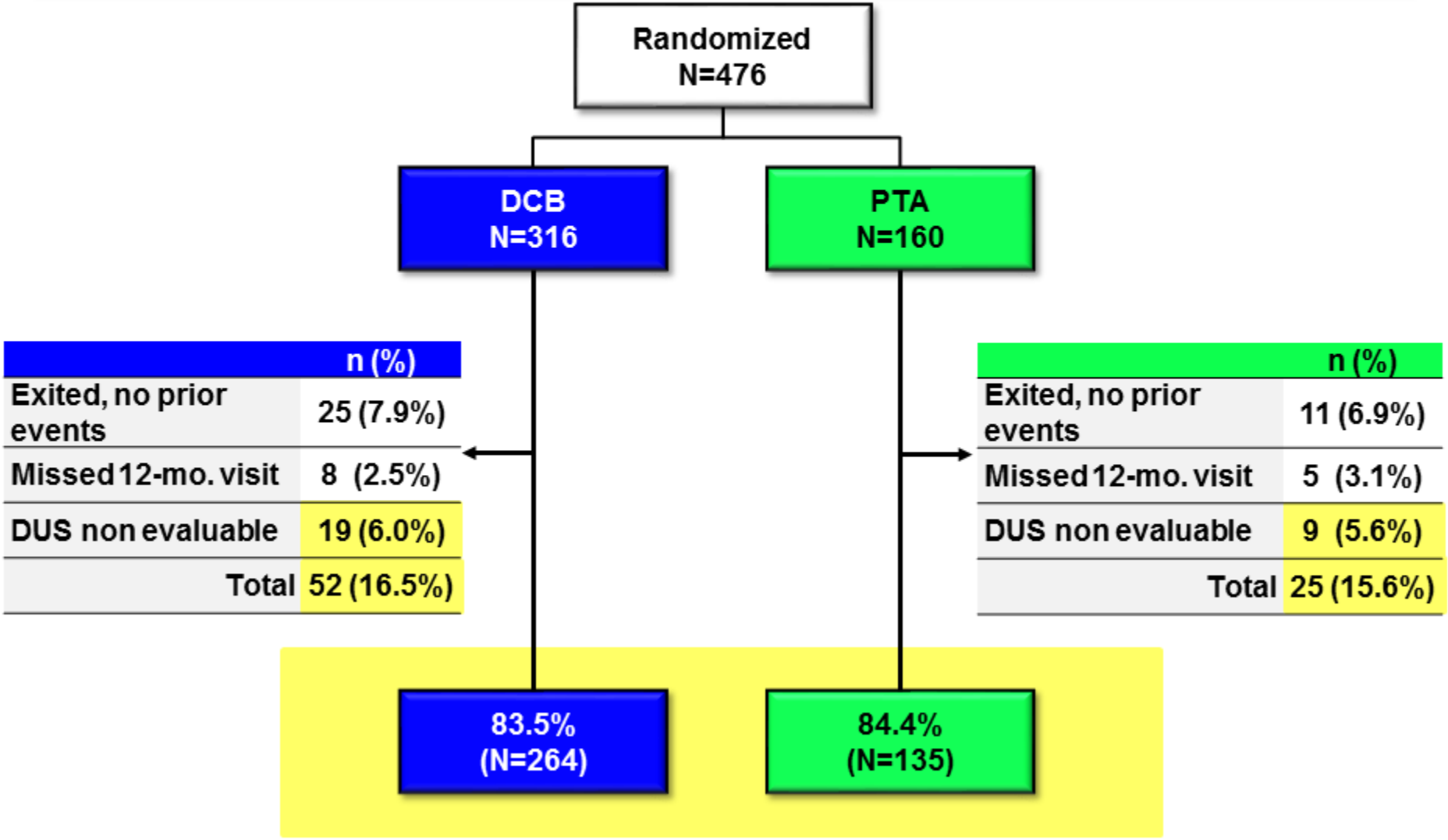
- DUS is a quantitative measure of stenosis
- Correlation between DUS and angiography for binary restenosis[1]
- PSVR ≥ 2.5 indicates 50% angiographic stenosis[1,2,3]

[1]Ranke, 1992 [2]Schlager, 2007 [3]Leiner, 2005

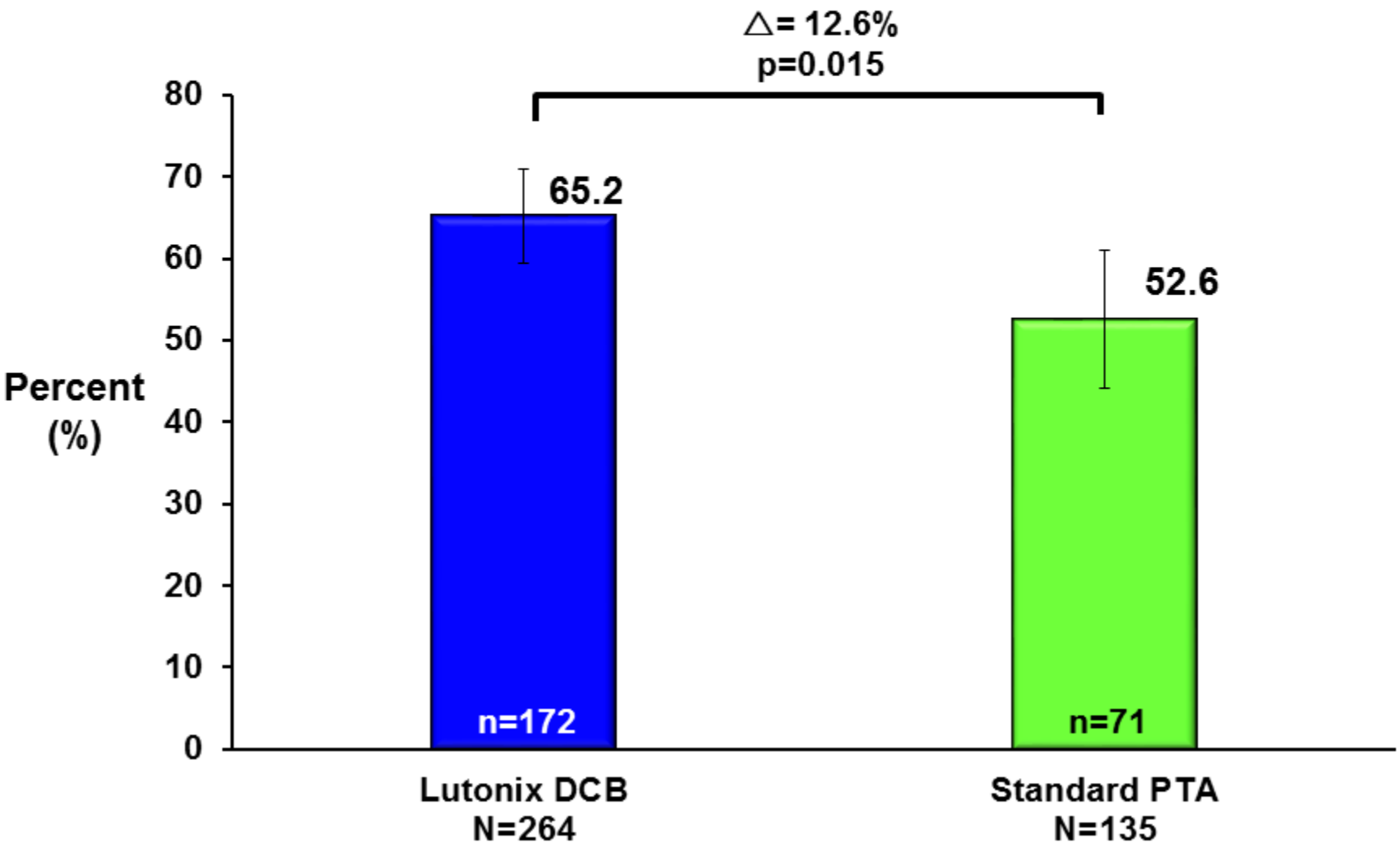
Efficacy Topics

- Use of duplex ultrasound (DUS) to assess primary patency
- Primary efficacy endpoint
- Supportive analyses
  - Subgroup results
  - Per Protocol
- Secondary endpoints

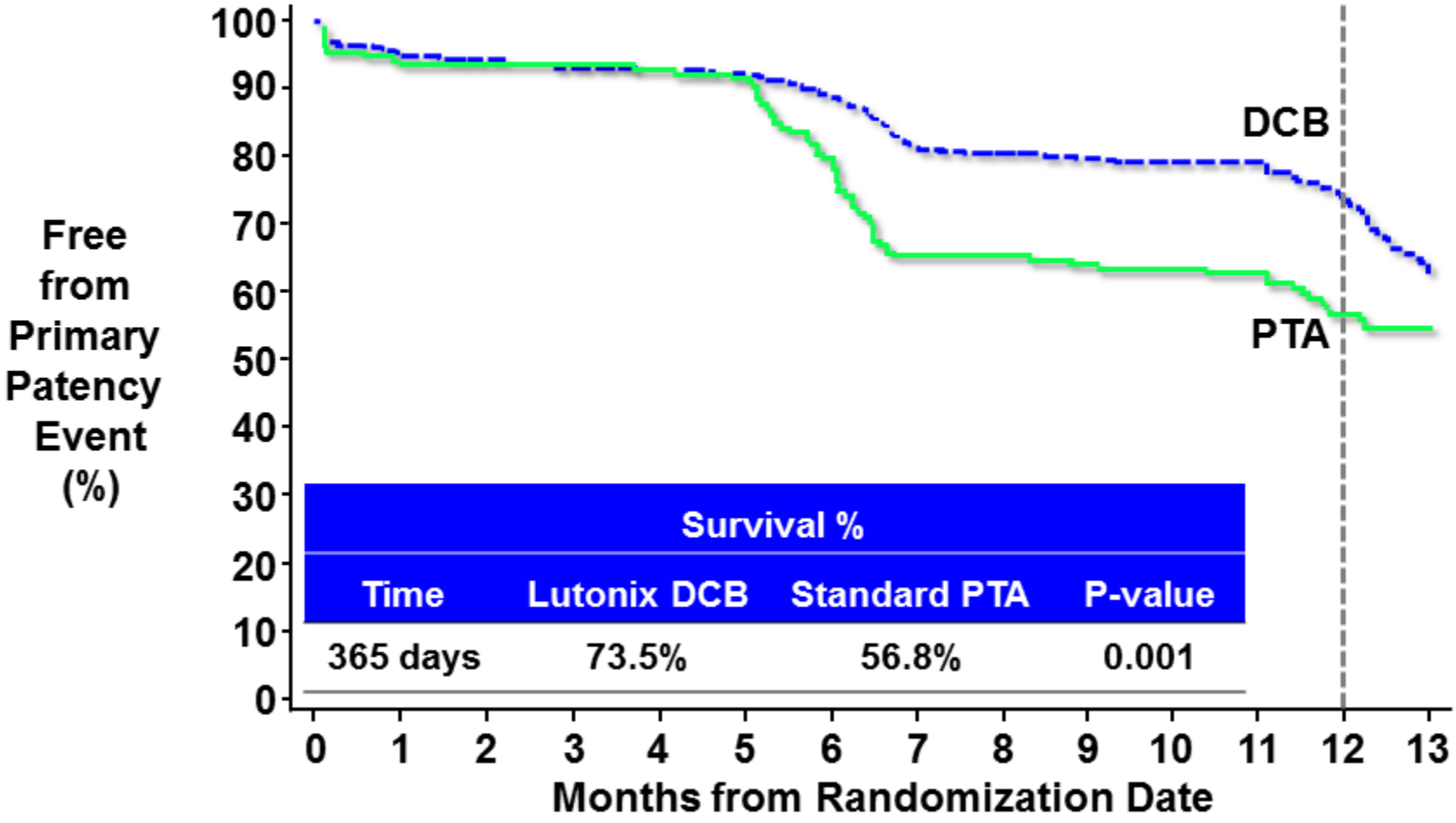
Evaluable Data for Efficacy



Efficacy Endpoint of Primary Patency Achieved



Primary Patency Kaplan-Meier



Lutonix DCB (N)	291	261	179
Standard PTA (N)	146	116	69

Duplex Ultrasound Results Correlate with Clinical Outcomes

Table 1 – TLR percentage at 12M based on DUS result at 6M

	Stenosis* (n/N)	Patent (n/N)	P-value
TLR at 12M Based on DUS Result at 6m	34.5% (29/84)	3.8% (12/318)	<0.001

Table 2 – Absolute Rutherford Class at 12M based on DUS result at 12M

	Stenosis* Mean +/- SD (N) Median (Range)	Patent Mean +/- SD (N) Median (Range)	P-value
Rutherford Class by DUS Result at 12M	1.1 ± 1.2 (109) 1.0 (0.0, 4.0)	0.8 ± 1.0 (262) 0.0 (0.0, 4.0)	0.002

*Core lab adjudicated stenosis PSVR > 2.5

Efficacy Topics

- Use of duplex ultrasound (DUS) to assess primary patency
- Primary efficacy endpoint
- Supportive analyses
  - Subgroup results
  - Per Protocol
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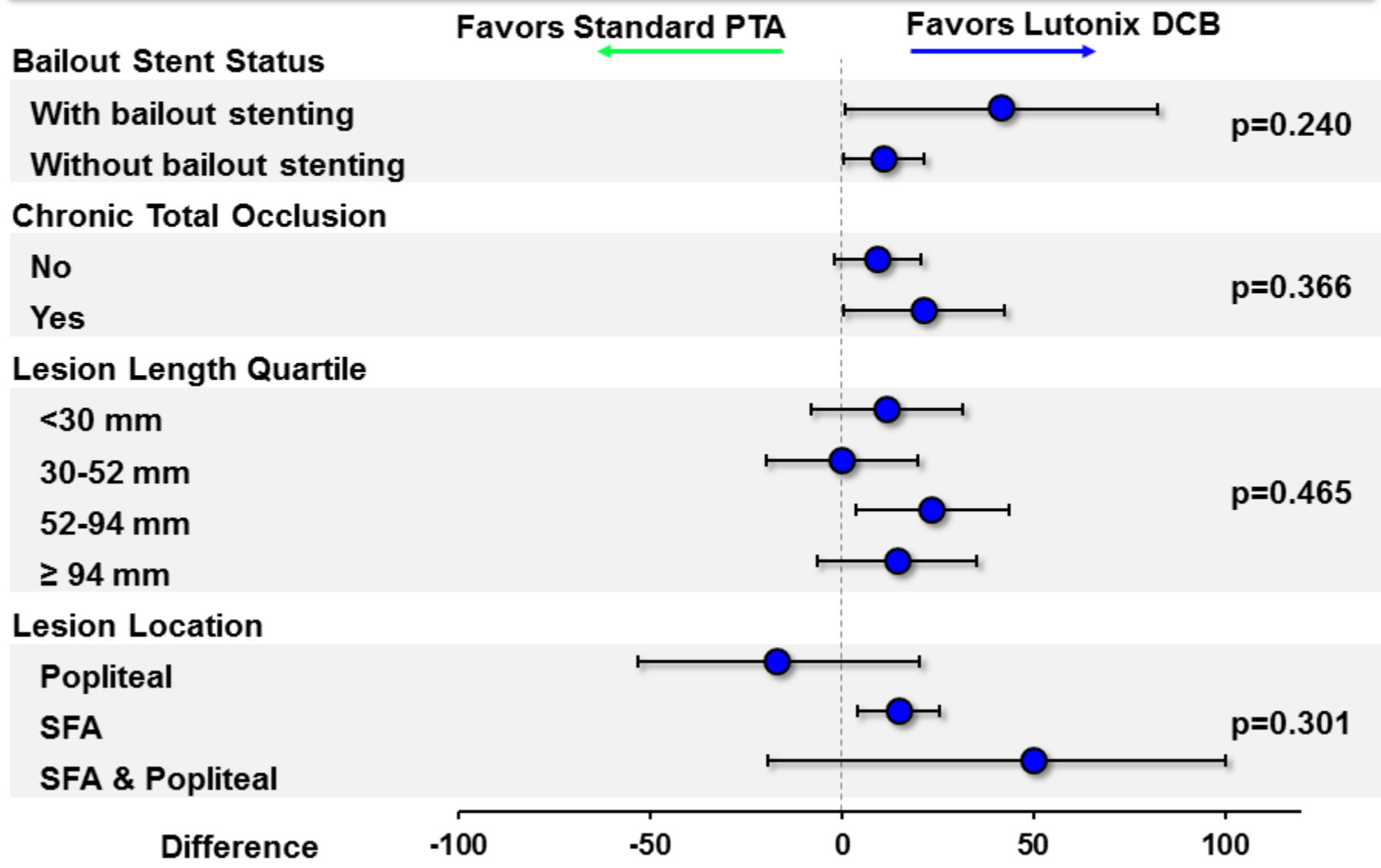
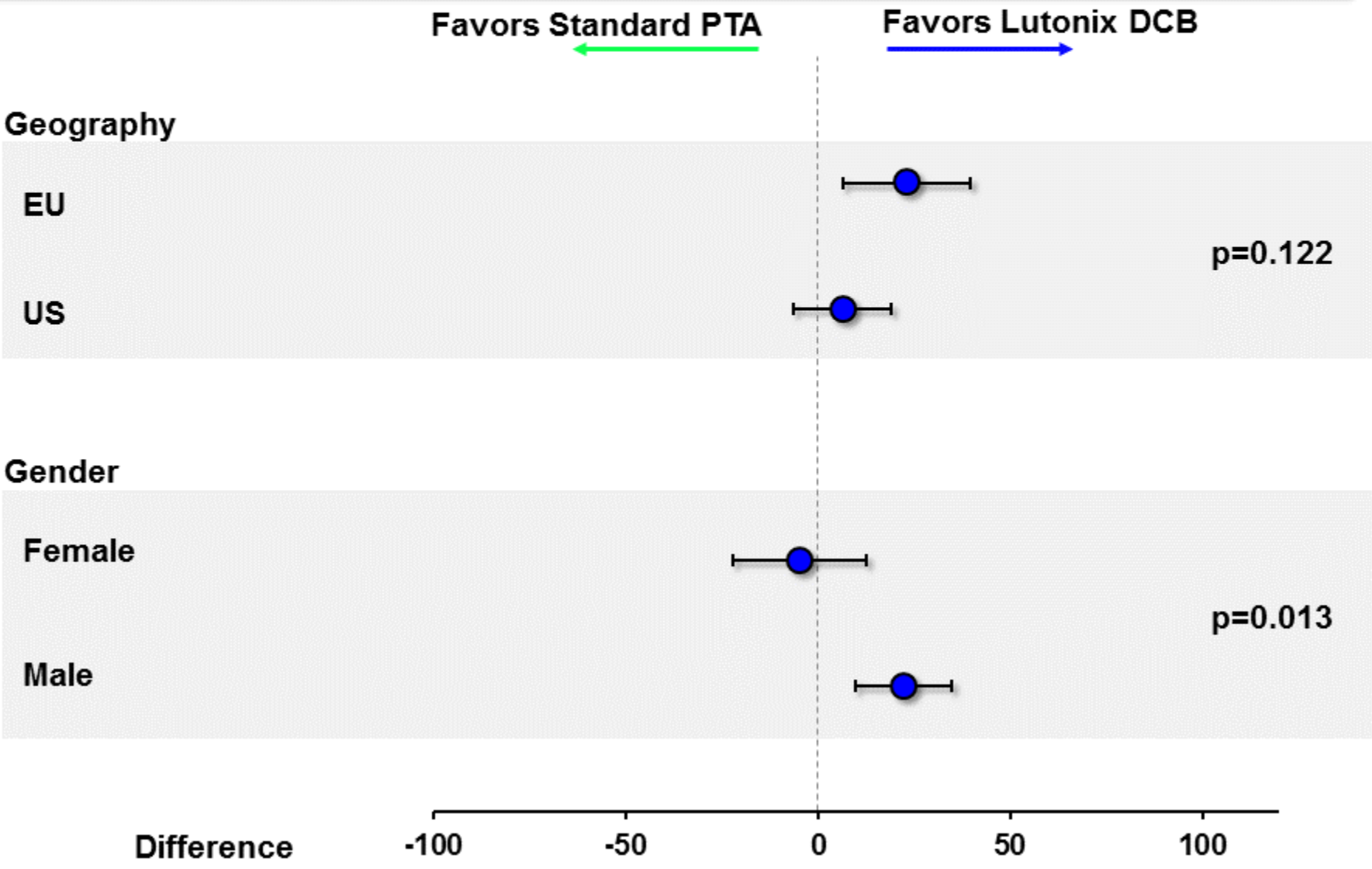
Supportive Analyses

- Generally underpowered
- Loss of balance from randomization
- Usually not statistically significant
- Trend in same direction as primary endpoint

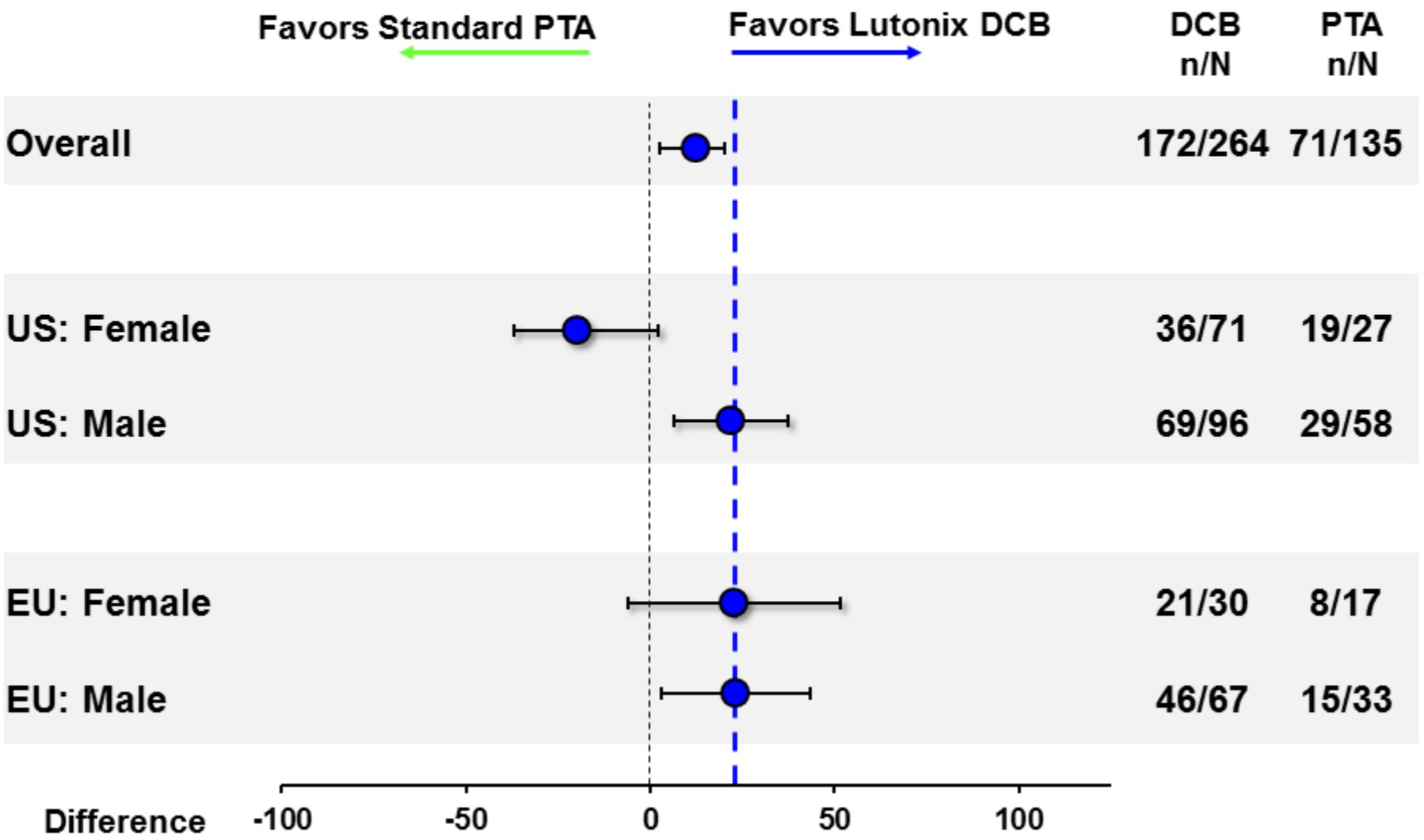
Majority of Subgroups Favor Lutonix DCB



Majority of Subgroups Favor Lutonix DCB for Efficacy



Primary Efficacy Results by Gender and Geography



Post-hoc three-way interaction of geography and gender was significant (p=0.010)

Per Protocol Results

Per Protocol Reasons For Exclusion

	Lutonix DCB N=316	Standard PTA N=160
Assigned Treatment Not Given	0.0%	0.0%
No Pre-dilatation	0.0%	0.0%
Outflow Artery Treatment	0.6%	1.3%
Site Reported Lesion >15 cm	0.0%	0.0%
Core Lab Determined Geographic Miss	7.6%	21.9%

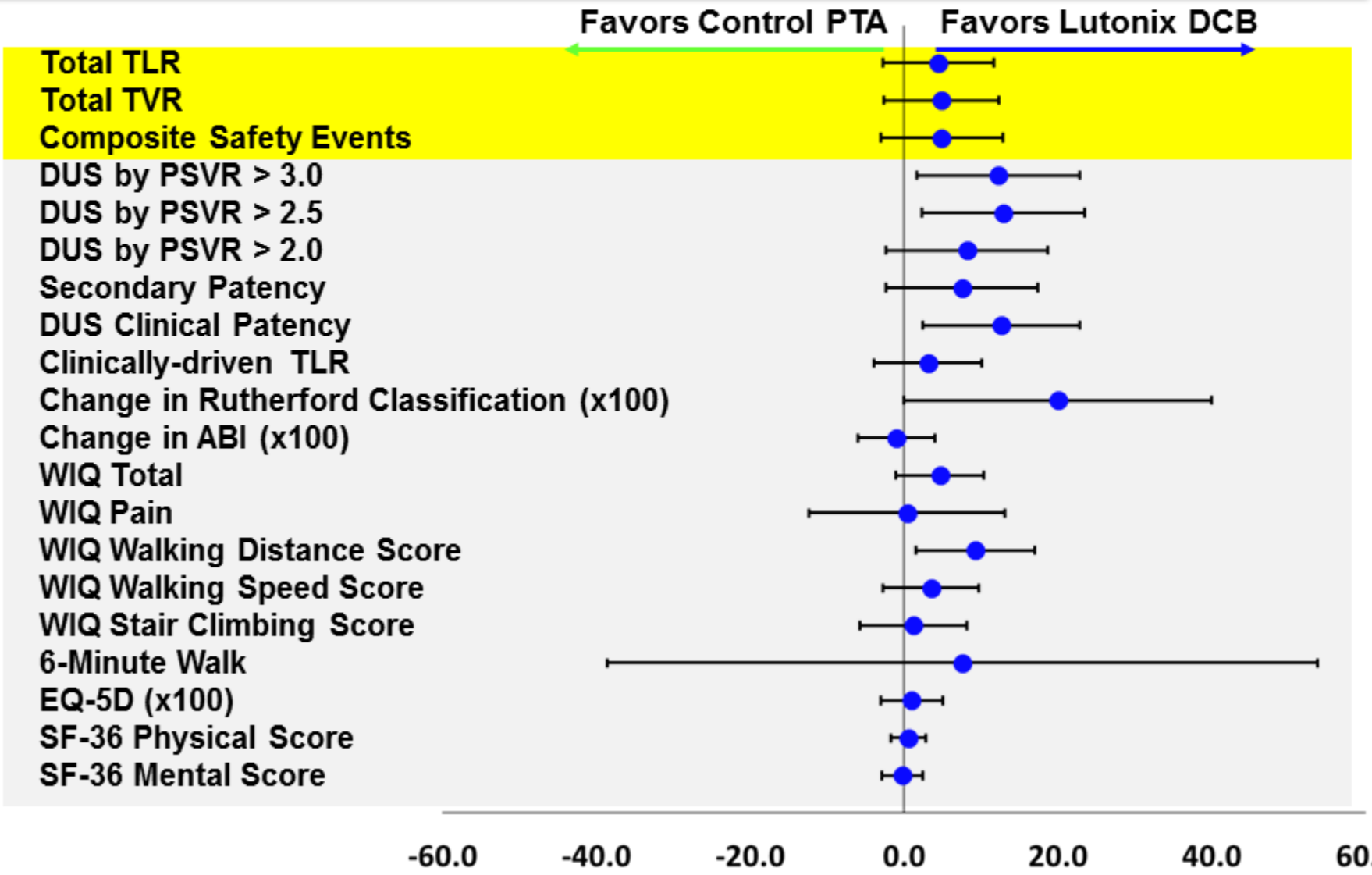
Primary Patency for Per-Protocol Populations

Population	Lutonix DCB %(n/N)	Standard PTA %(n/N)	Difference % [95% CI]	P-value
ITT	65.2% (172/264)	52.6% (71/135)	12.6 [2.4, 22.8]	0.015
Per Protocol	**65.3% (160/245)**	**56.0% (56/100)**	**9.3% [-2.1, 20.7]**	**0.107**
Post-hoc Per Protocol	**67.6% (152/225)**	**52.2% (60/115)**	**15.4% [4.4, 26.4]**	**0.006**

Efficacy Topics

- Use of duplex ultrasound (DUS) to assess primary patency
- Primary efficacy endpoint
- Supportive analyses
  - Subgroup results
  - Per Protocol
- Secondary endpoints

Summary of Secondary Endpoints at 12 Months



Freedom from TLR

Visit	Lutonix DCB % (n/N)	Standard PTA % (n/N)	Difference % [95% CI]
6 Months	94.0% (280/298)	94.0% (142/151)	-0.1% [-4.7, 4.6]
12 Months	87.7% (250/285)	83.2% (119/143)	4.5% [-2.7, 11.7]

Unique study design aspects

- Clinician blinding
- Blinding to DUS results at follow-up
- Bailout stenting not a TLR

Study Design was Effective in Controlling Bias

Efficacy Event	Lutonix DCB % (n/N Failures)	Standard PTA % (n/N Failures)
% of patients with patency failure who had TLR	38.0% (35/92)	37.5% (24/64)
% of patients with worsening clinical status* who had TLR	44.9% (35/78)	48.0% (24/50)

* Unimproved from baseline Rutherford Class or TVR

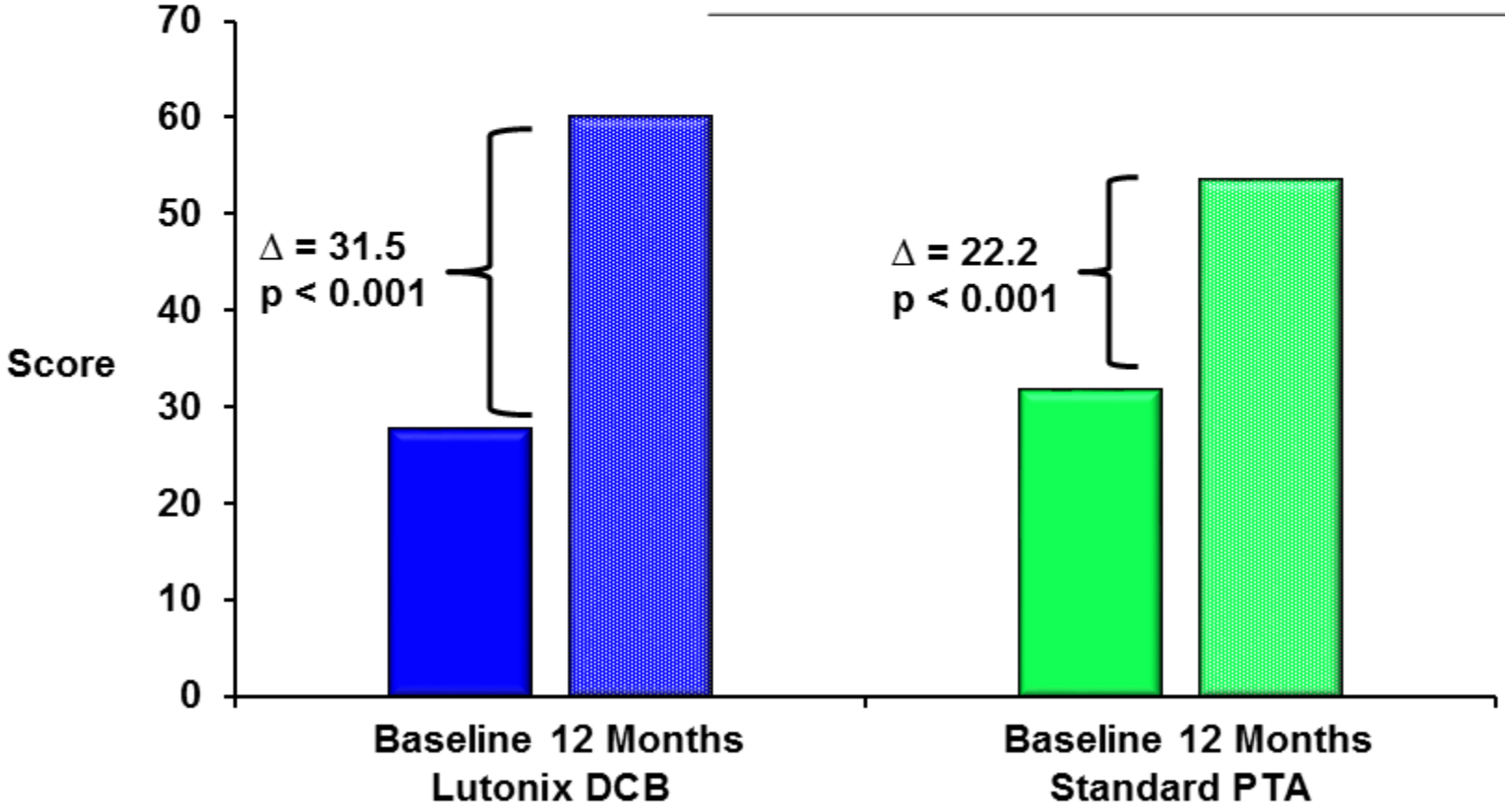
Additional Analyses

Walking Impairment Distance

Distance	Degree of Difficulty				
	None	Slight	Some	Much	Unable
1. Walking indoors such as around your home?	4	3	2	1	0
2. Walking 50 feet?	4	3	2	1	0
3. Walking 150 feet (1/2 block)?	4	3	2	1	0
4. Walking 300 feet (1 block)?	4	3	2	1	0
5. Walking 600 feet (2 blocks)?	4	3	2	1	0
6. Walking 900 feet (3 blocks)?	4	3	2	1	0
7. Walking 1500 feet (5 blocks)?	4	3	2	1	0

WIQ Walking Distance

Lutonix DCB	Standard PTA	P-value
31.5	22.2	0.017

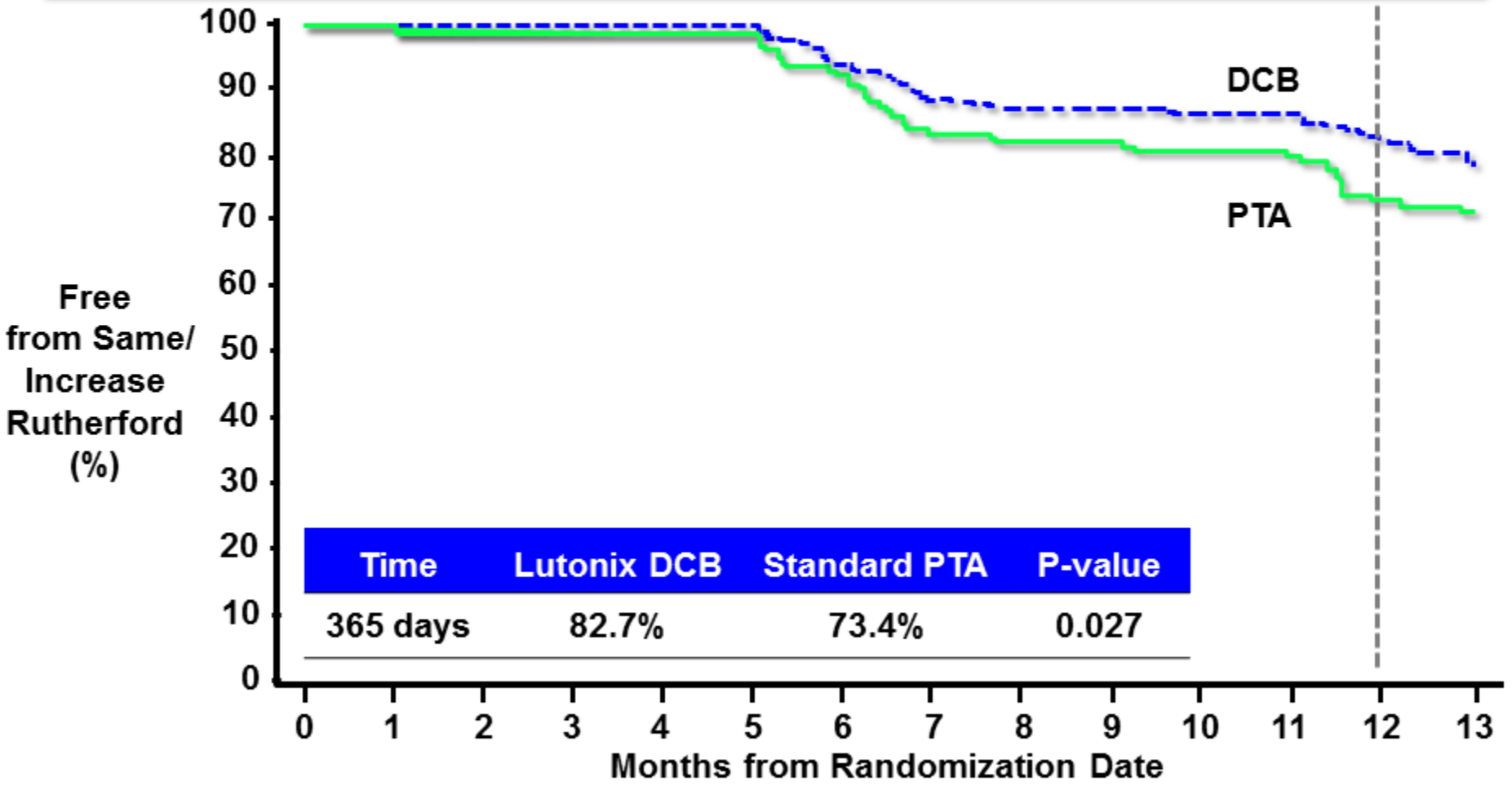


p-values not adjusted for multiplicity

Rutherford Class Definitions

Class	Definition
Class 0	Asymptomatic
Class 1	Mild claudication
Class 2	Moderate claudication
Class 3	Severe claudication
Class 4	Ischemic rest pain
Class 5	Minor tissue loss
Class 6	Major tissue loss

Sustained Improvement in Rutherford Class

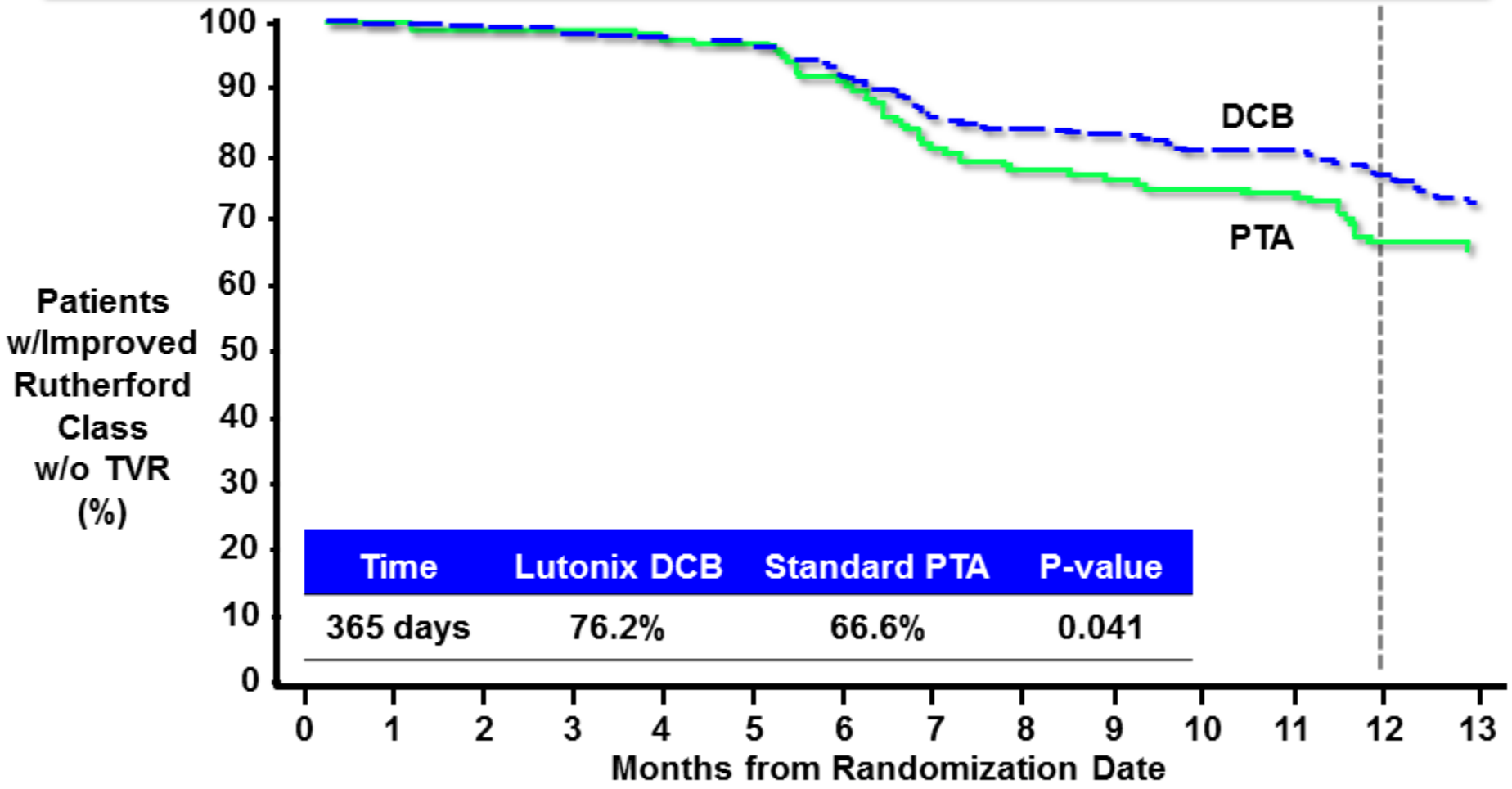


Time	Lutonix DCB	Standard PTA	P-value
365 days	82.7%	73.4%	0.027

Lutonix DCB (N)	307	276	206
Standard PTA (N)	154	136	91

p-values not adjusted for multiplicity

Sustained Improvement in Rutherford Class without Reintervention

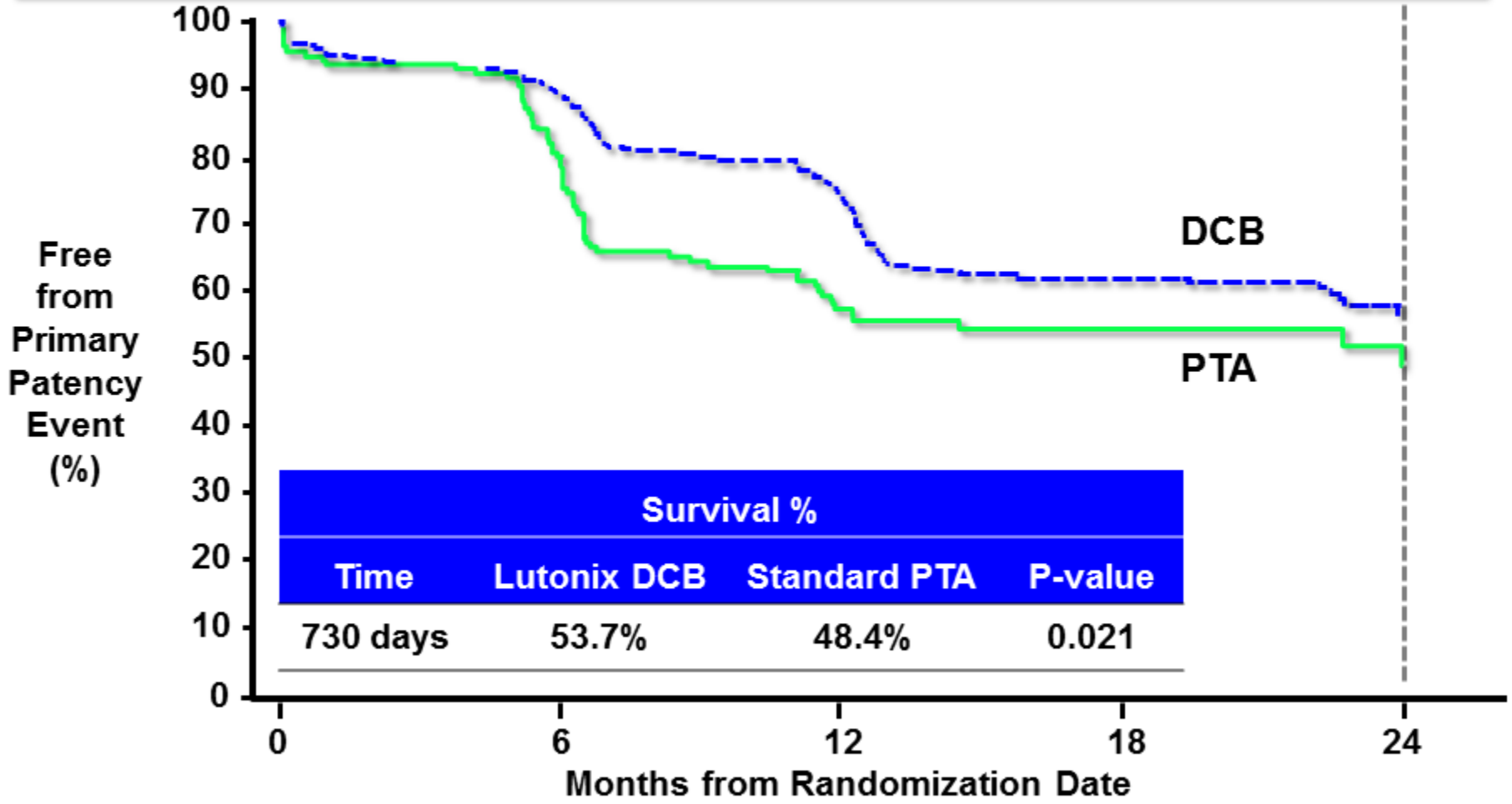


p-values not adjusted for multiplicity

Primary Patency by Lesion Length

Variable	Subset	Lutonix DCB % (n/N)	Standard PTA % (n/N)	Difference
Lesion Length ≥ 14 cm	No	66.8% (165/247)	52.3% (67/128)	14.5%
	Yes	37.5% (6/16)	57.1% (4/7)	-19.6%
Lesion Length Quartile (mm)	Q1: < 30	72.3% (47/65)	60.6% (20/33)	11.7%
	Q2: 30 – 52	64.7% (44/68)	64.7% (22/34)	0.0%
	Q3: 52 – 94	69.2% (45/65)	45.7% (16/35)	23.5%
	Q4: ≥ 94	53.8% (35/65)	39.4% (13/33)	14.5%

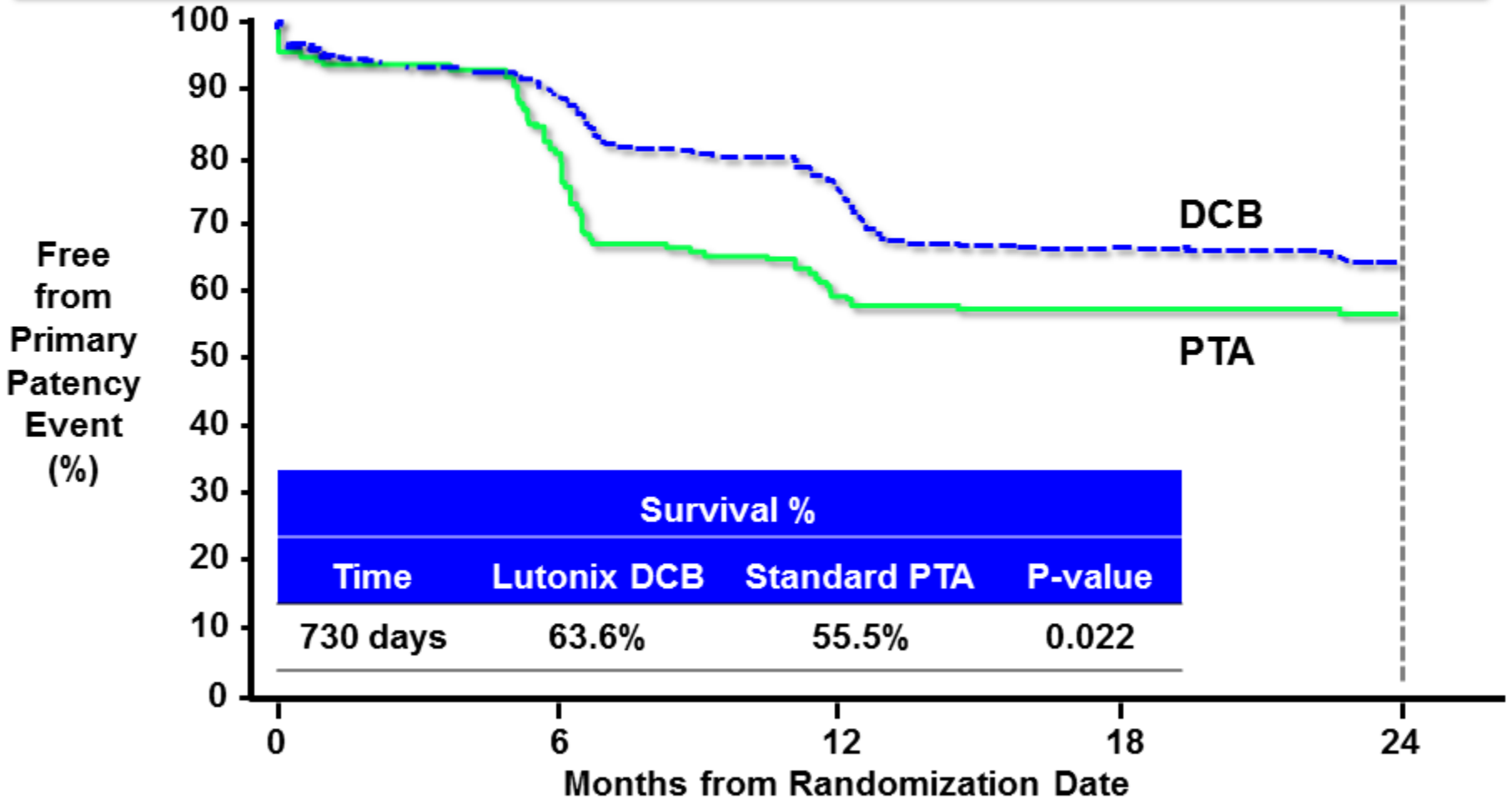
Primary Efficacy Endpoint Through 24 Months (Preliminary Data)



Survival %			
Time	Lutonix DCB	Standard PTA	P-value
730 days	53.7%	48.4%	0.021

Lutonix DCB (N)	291	179	26
Standard PTA (N)	146	69	14

Primary Efficacy Endpoint Through 24 Months (Non-exited Pts. Not Censored)



Survival %			
Time	Lutonix DCB	Standard PTA	P-value
730 days	63.6%	55.5%	0.022

Lutonix DCB (N)	296	215	173
Standard PTA (N)	149	89	77

Analysis not previously reviewed by FDA

Efficacy Summary

- Primary endpoint of primary patency met
  - 12.6% greater patency
  - Lutonix DCB 65.2% vs standard PTA 52.6% (p=0.015)
- Supportive and subgroup analyses results generally consistent with primary endpoint analysis
- Additional analyses showed improvement in
  - Walking Distance
  - Sustained Rutherford Class

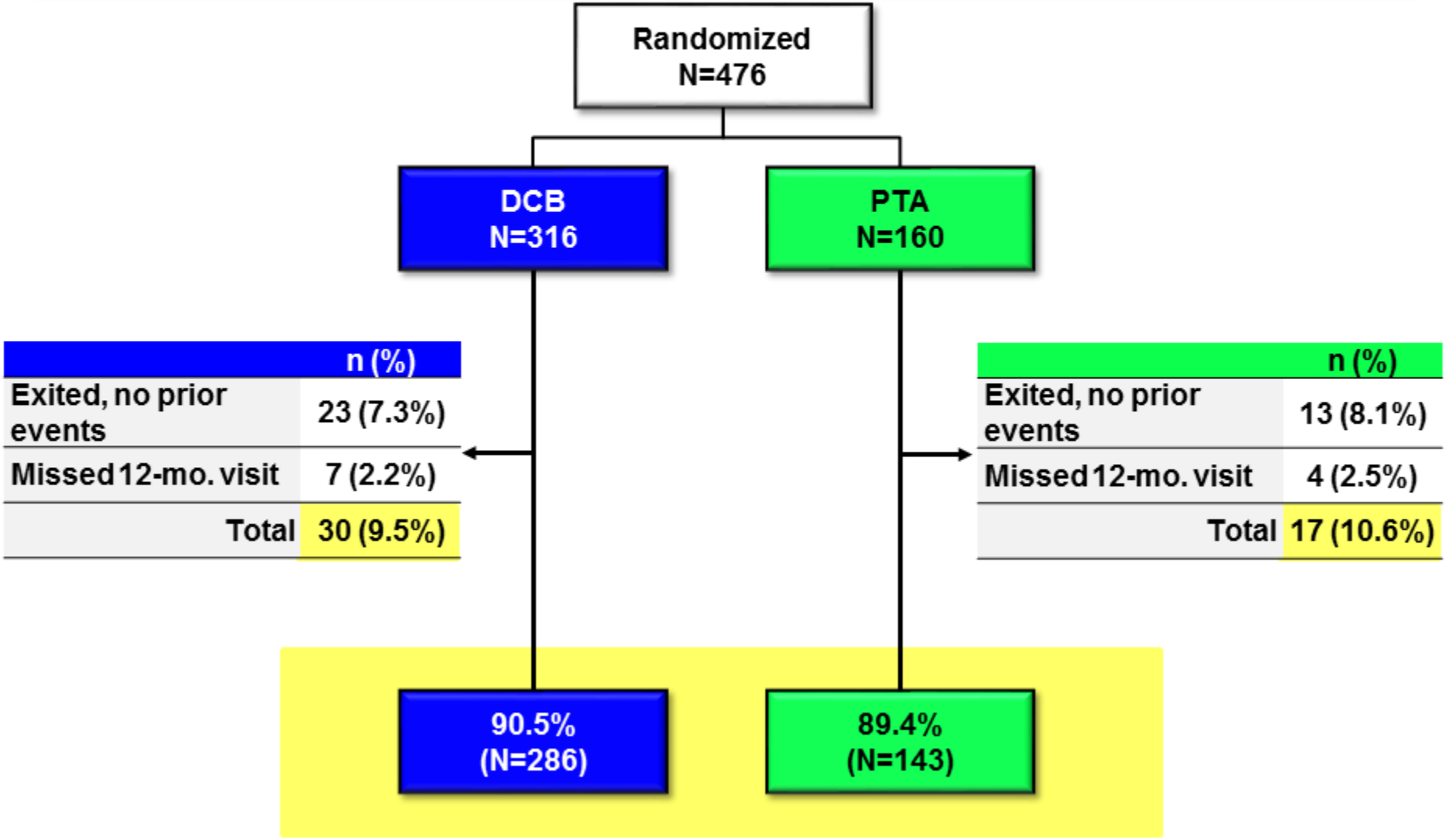
Safety

Gary Ansel, MD
System Medical Chief, Vascular Services
Ohio Health/Riverside Methodist Hospital

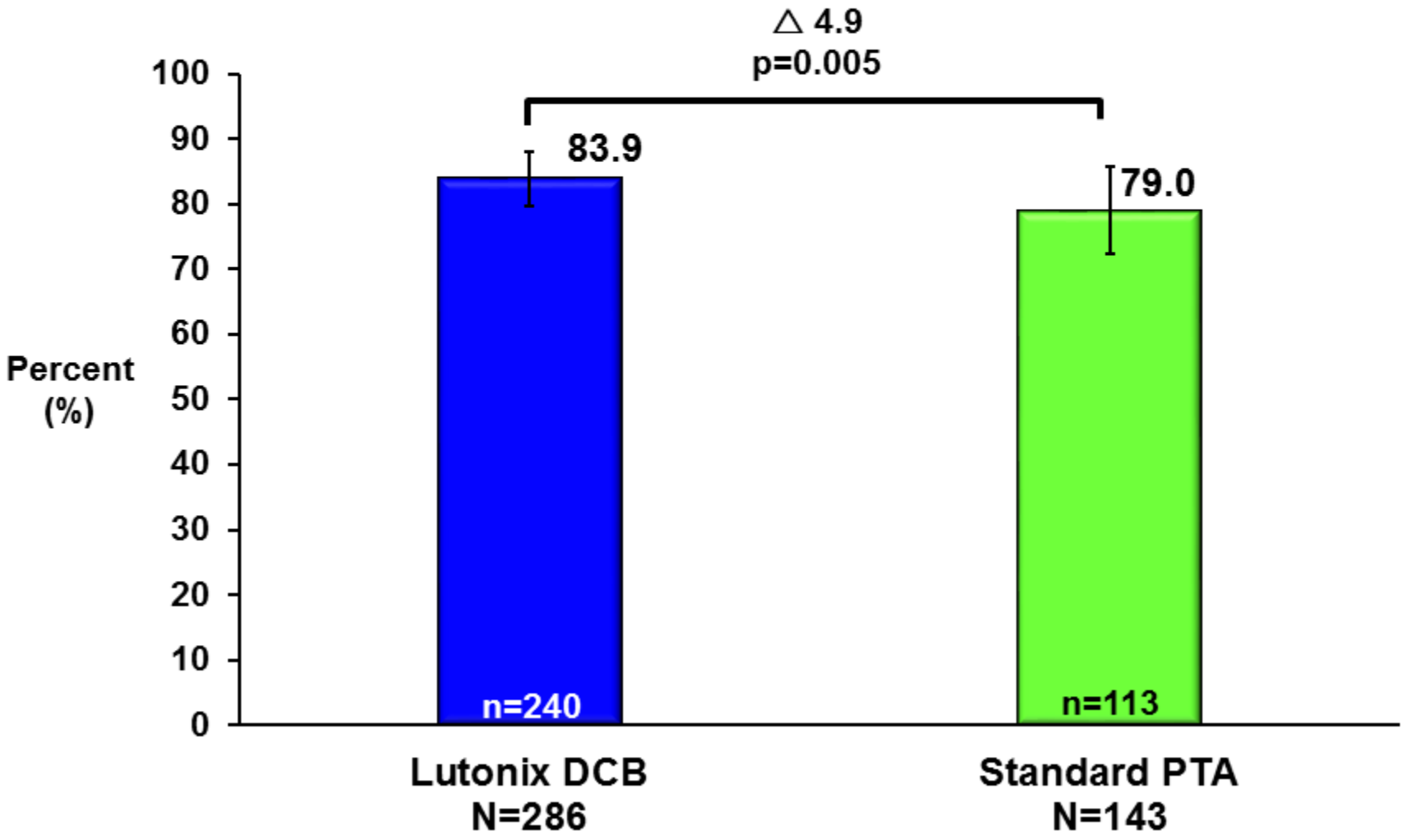
Primary Composite Safety Endpoint

- 12-month composite safety endpoint freedom from
  - All cause index limb re-intervention
  - Index limb amputation
  - Index limb-related death
  - All-cause perioperative death
- Non-inferiority, with 5% margin

Evaluable Data for Safety



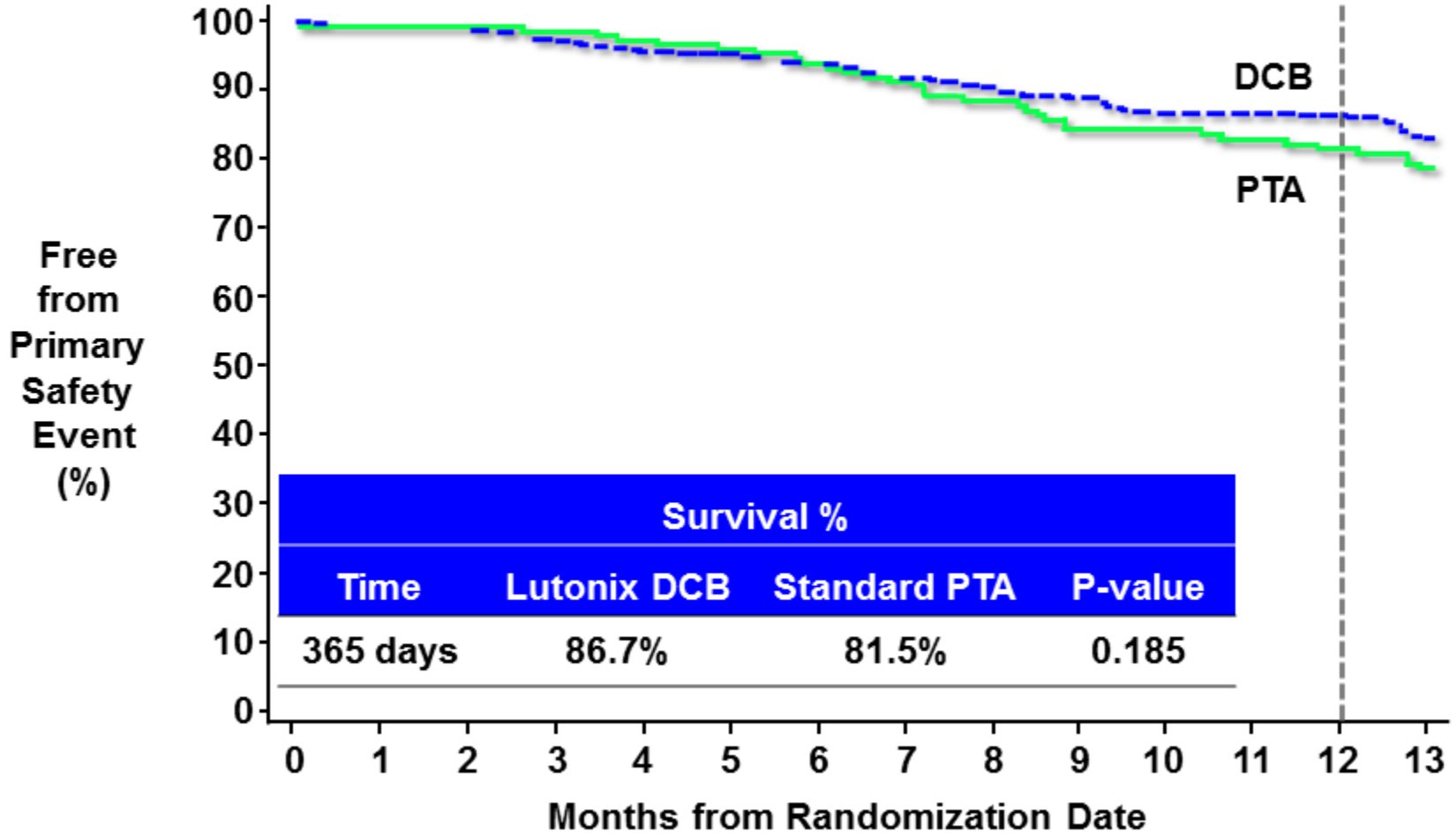
Freedom from Primary Safety Event



Primary Safety Events

Safety Event *(Patients may have > 1 event)*	Lutonix DCB % (n/N)	Standard PTA % (n/N)
Perioperative (≤ 30) Death	0.0% (0/308)	0.0% (0/155)
Index Limb Related Death at 12 months	0.0% (0/285)	0.0% (0/140)
Amputation at 12 months	0.3% (1/286)	0.0% (0/140)
AV Fistula Surgery at 12 months	0.4% (1/285)	0.0% (0/140)
Surgical Bypass at 12 months	0.7% (2/285)	0.7% (1/140)
Total TLR at 12 months	12.3% (35/285)	16.8% (24/143)
Non-TLR TVR at 12 months	1.1% (3/285)	1.4% (2/143)
Index Limb Interventions in Non-target Vessels at 12 months	2.1% (6/285)	2.9% (4/140)

Freedom from Primary Safety Event

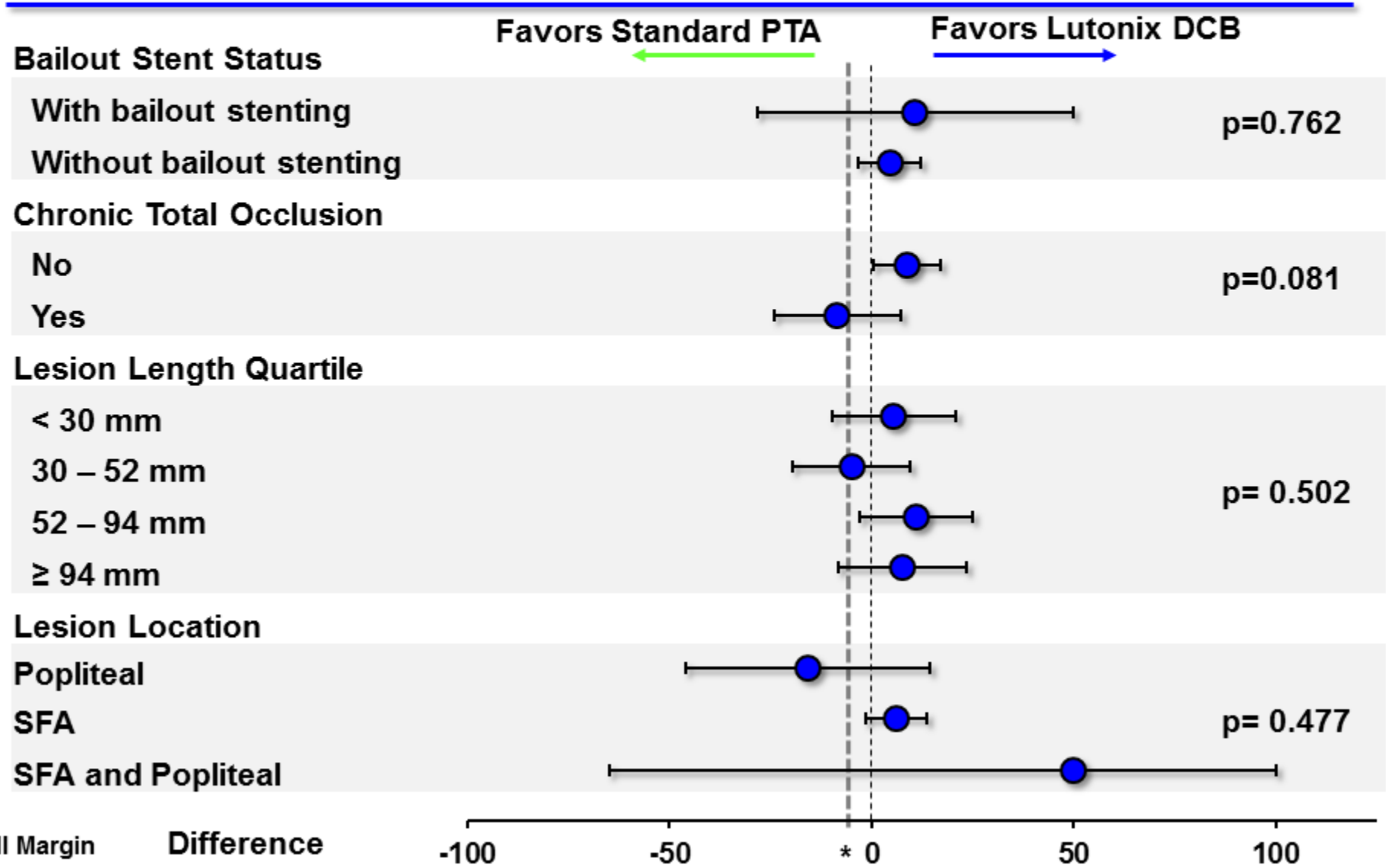


Survival %			
Time	Lutonix DCB	Standard PTA	P-value
365 days	86.7%	81.5%	0.185

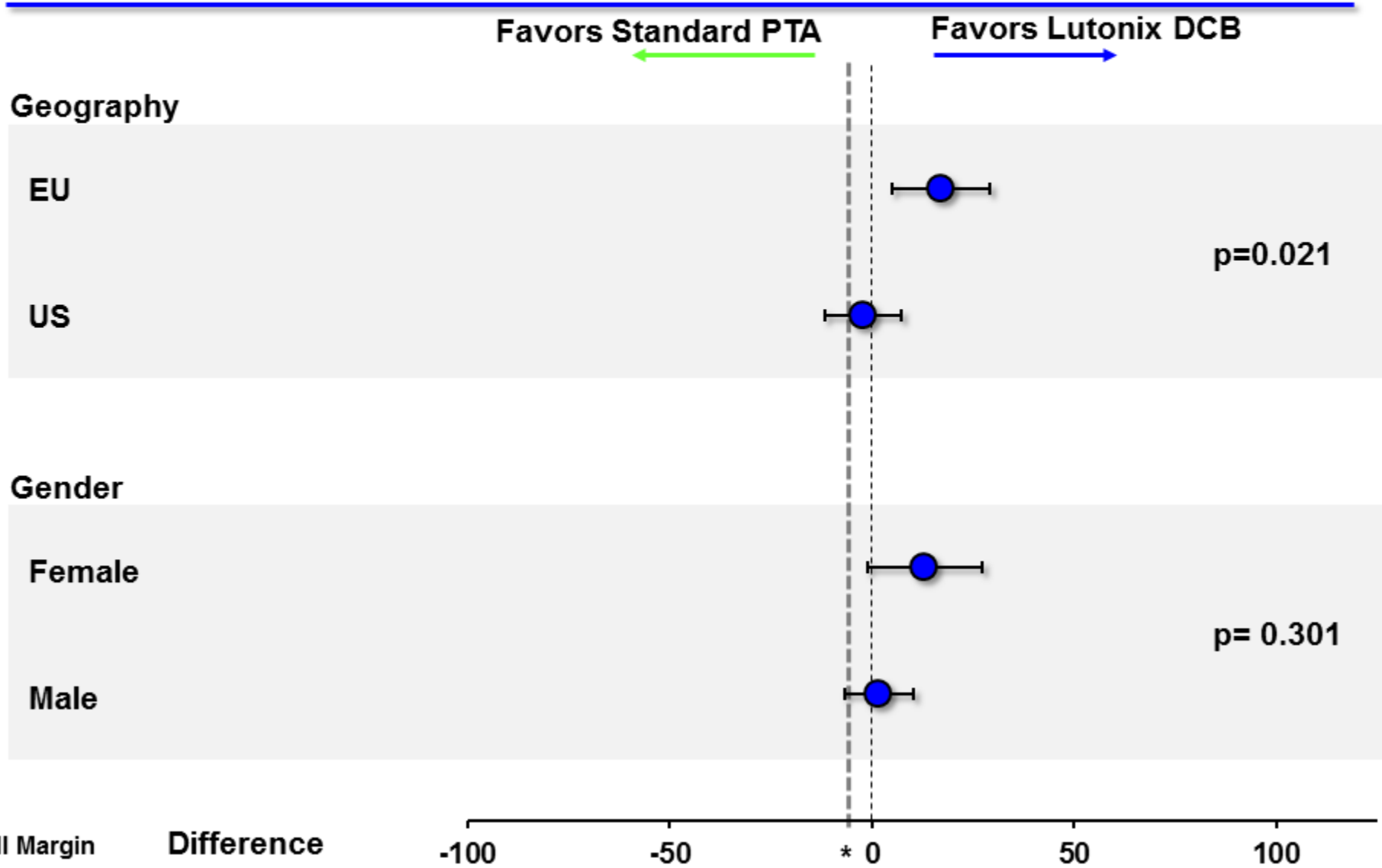
Lutonix DCB (N)	305	276	183
Standard PTA (N)	154	138	88

Supportive Analyses

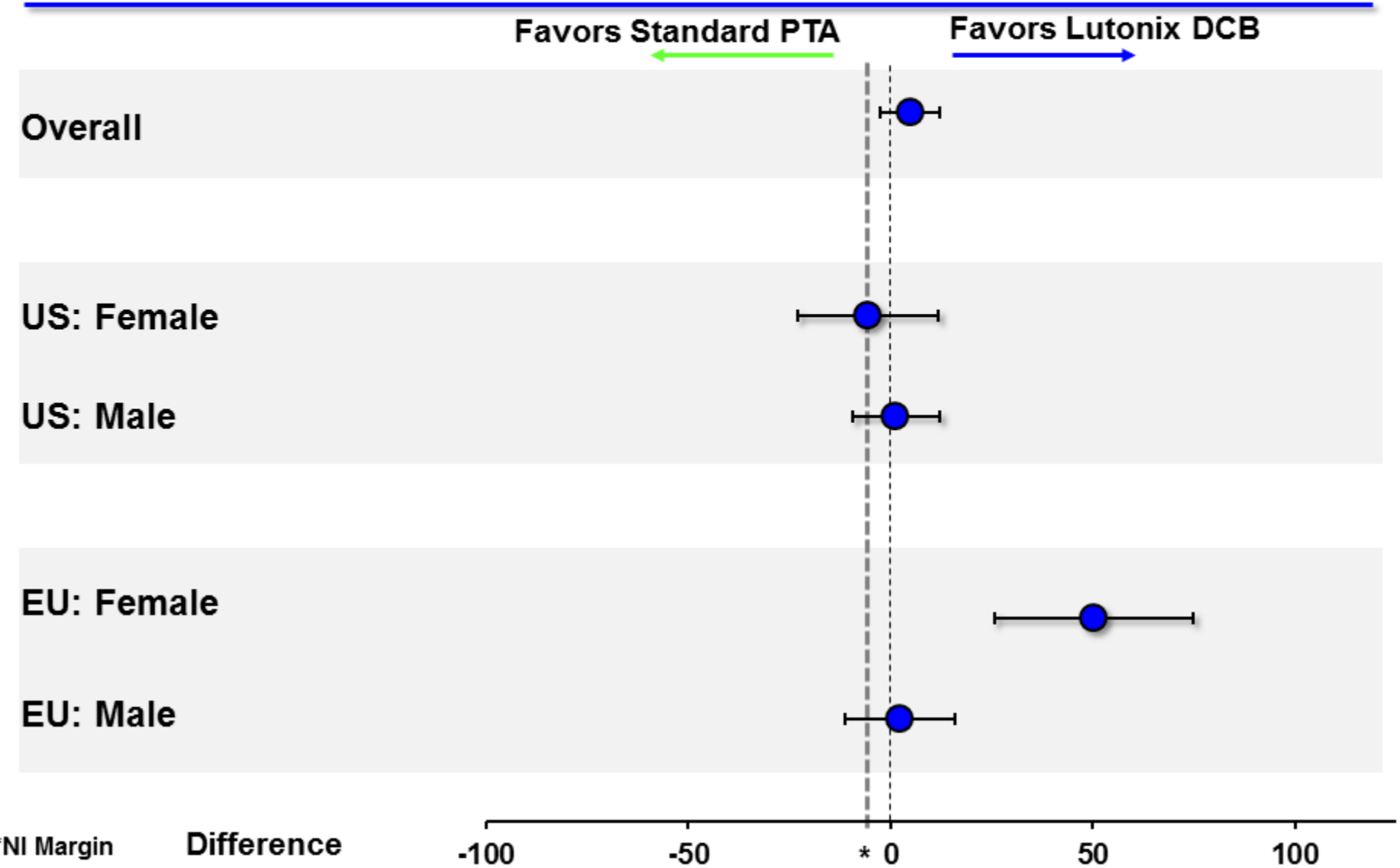
Consistent Noninferiority By Lesion Subgroup for Primary Safety Endpoint



Geography and Gender Subgroups: Primary Safety Endpoint



Primary Safety Rate by Gender by Region



Primary Safety for Per Protocol Populations

Population	Lutonix DCB % (n/N)	Standard PTA % (n/N)	Difference % [95% CI]	P-value
ITT	83.9% (240/286)	79.0% (113/143)	4.9% [-2.6, 12.3]	0.005
Per Protocol	**83.7% (221/264)**	**83.0% (88/106)**	**0.7% [-7.3, 8.7]**	**0.080**
Post-hoc Per Protocol	**84.2% (202/240)**	**79.3% (96/121)**	**4.8% [-3.2, 12.9]**	**0.008**

Secondary Safety Endpoints

Other Secondary Safety Endpoints at 12 Months

Outcome	Lutonix DCB n/N (%)	Standard PTA n/N (%)	Difference % [95% CI]	P-value
Composite Safety Events	240/286 (83.9%)	113/143 (79.0%)	4.9% [-3.0, 12.8]	0.215
Death	7/290 (2.4%)	4/144 (2.8%)	-0.4% [-3.6, 2.8]	0.822
Major Amputation	1/286 (0.3%)	0/140 (0.0%)	0.3% [-0.3, 1.0]	0.372
Amputation-free Survival	283/290 (97.6%)	140/144 (97.2%)	0.4% [-2.8, 3.6]	0.822
Total TVR	38/285 (13.3%)	26/142 (18.3%)	-4.8% [-12.3, 2.6]	0.190
Reintervention for Thrombosis	1/285 (0.4%)	1/140 (0.7%)	-0.4% [-1.9, 1.2]	0.618
Cardiovascular Hospitalizations	26/285 (9.1%)	10/140 (7.1%)	2.0% [-3.4, 7.4]	0.485
Major Vascular Complications	18/285 (6.3%)	7/142 (4.9%)	1.4% [-3.2, 5.9]	0.560

Deaths Through 12 Months

	Lutonix DCB (n=316)		Standard PTA (N=160)	
	N (%)	Time to event Median (min, max)	N (%)	Time to event Median (min, max)
Total*	7 (2.4%)	267.0 (53.0, 382.0)	4 (2.8%)	248.5 (121.0, 314.0)
Cancer	1 (0.3%)		2 (1.3%)	
Cardiovascular/ unknown	5 (1.6%)		2 (1.3%)	
Ischemic stroke	1 (0.3%)		0 (0.0%)	

*No deaths adjudicated by the CEC as related to the device, procedure or index limb

Serious Adverse Event Details

SAEs Occurring in ≥ 2% of Patients

Event code	Lutonix DCB N=316 Patients n (%)	Standard PTA N=160 Patients n (%)
Total	160 (50.6%)	78 (48.8%)
Claudication	38 (12.0%)	26 (16.3%)
Restenosis of Non-study Vessel	22 (7.0%)	10 (6.3%)
Angina	13 (4.1%)	2 (1.3%)
Neoplasia	11 (3.5%)	8 (5.0%)
Other Clinical	9 (2.8%)	4 (2.5%)
Stroke (focal deficit lasting over 24 hours)	9 (2.8%)	1 (0.6%)
Target Extremity Pain	9 (2.8%)	4 (2.5%)
Pneumonia	7 (2.2%)	2 (1.3%)
Gastrointestinal Disorder	6 (1.9%)	6 (3.8%)
Target Vessel Injury/Dissection with Study Treatment	6 (1.9%)	6 (3.8%)
Restenosis of the Study Lesion	5 (1.6%)	6 (3.8%)
Orthopedic Injury	5 (1.6%)	4 (2.5%)

CEC Adjudicated as Possibly, Probably, or Highly Probably Device or Procedure or Drug Related

	All		CEC Adjudicated as Possible, Probably, Highly Probably					
			Device Related		Procedural Related		Drug Related	
	DCB	PTA	DCB	PTA	DCB	PTA	DCB	PTA
Angina	14 (4.4%)	3 (1.9%)	0	0	0	0	0	0
Stroke	9 (2.8%)	1 (0.6%)	0	0	0	0	0	0
CHF	6 (1.9%)	0 (0.0%)	0	0	0	0	0	0
COPD	5 (1.6%)	1 (0.6%)	0	0	0	0	0	0

- None adjudicated as Possibly, Probably, or Highly Probably Device, Procedure, or Drug Related
- REACH[1] study of symptomatic PAD patients (N=8581)
  - Unstable angina = 4.5%
  - Non-fatal stroke = 1.9%
  - CHF admissions = 4.4%

[1]Steg, 2007

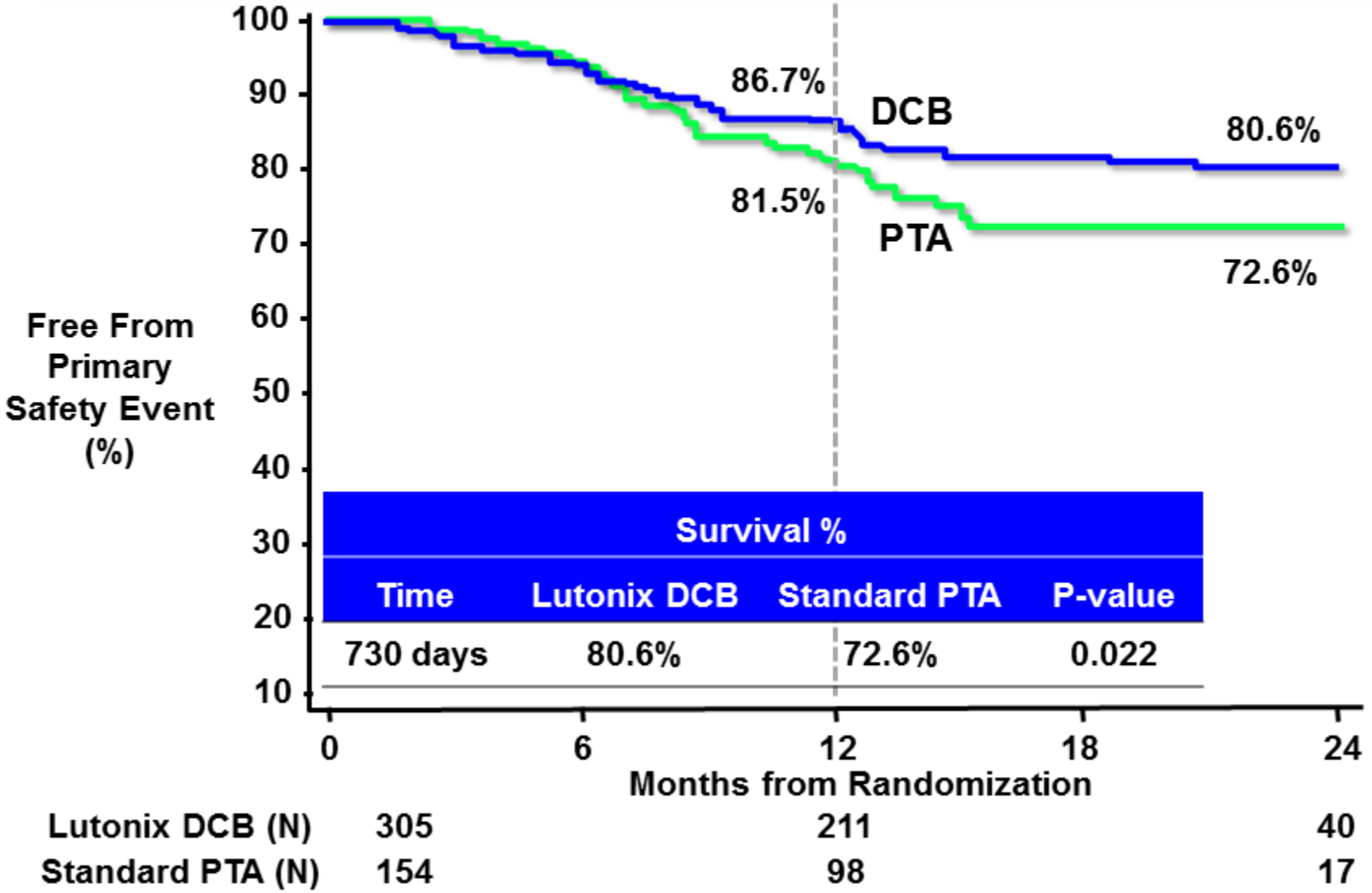
Device-Related SAE

Event code	Lutonix DCB N=316 Patients n (%)	Standard PTA N=160 Patients n (%)
Total	34 (10.8%)	27 (16.9%)
Claudication	14 (4.4%)	13 (8.1%)
Target Vessel Injury/Dissection with Study Treatment	6 (1.9%)	6 (3.8%)
Target Extremity Pain	6 (1.9%)	2 (1.3%)
Restenosis Of The Study Lesion	4 (1.3%)	2 (1.3%)
Access Site: Significant Hemorrhage req Transfusion	3 (0.9%)	0 (0.0%)
Target Vessel Injury/Dissection with Post-treatment	1 (0.3%)	2 (1.3%)
Distal Embolization with Study Treatment	1 (0.3%)	1 (0.6%)
Clot/Thrombus Formation (Thrombosis)	1 (0.3%)	2 (1.3%)
Restenosis of the Non-study Vessel	1 (0.3%)	0 (0.0%)
Non-target Extremity Revascularization	1 (0.3%)	0 (0.0%)
Target Extremity Ischemic Ulcer-new	1 (0.3%)	0 (0.0%)
Bilateral Lower Extremity Pain	1 (0.3%)	0 (0.0%)
Distal Embolization with Post-treatment	0 (0.0%)	1 (0.6%)

Procedure-Related SAEs Occurring in ≥ 1% of Patients

Event code	Lutonix DCB N=316 Patients n (%)	Standard PTA N=160 Patients n (%)
Total	47 (14.9%)	32 (20.0%)
Claudication	18 (5.7%)	17 (10.6%)
Target Vessel Injury/Dissection with Study Treatment	6 (1.9%)	6 (3.8%)
Target Extremity Pain	6 (1.9%)	3 (1.9%)
Access Site: Pseudoaneurysm	4 (1.3%)	1 (0.6%)
Restenosis of the Study Lesion	4 (1.3%)	2 (1.3%)
Target Vessel Injury/Dissection with Post-treatment	1 (0.3%)	2 (1.3%)
Clot/Thrombus Formation (Thrombosis)	1 (0.3%)	2 (1.3%)

Primary Safety Endpoint Through 24-Months (Preliminary Data)



Overview of SAEs Through 24 Months

	Lutonix DCB N=316		Standard PTA N=160	
	Events (n)	Patients with Event (%)	Events (n)	Patients With Event (%)
SAEs	338	53.5%	169	50.0%
Device-related	43	11.1%	33	18.1%
Procedure-related	62	15.2%	41	21.3%
Deaths	16	5.0%	7	4.4%

Safety Registry

- Extension of the LEVANT 2 Lutonix DCB arm
  - Same protocol as LEVANT 2
  - Same follow-up duration, out to 5 years
  - Enrollment completed of 657 patients
  - All events collected and adjudicated by the CEC

Detection of Rare Adverse Events

- Prospective Statistical Plan (negotiated with FDA)
- Primary endpoint: rate of unanticipated device- or drug-related AEs over time assessed at 1, 6, 12, 24, 36, 48 and 60 months

Potential Observed Rare Event	Sample Size	95% CI Upper Limit	# of Events Detectable at >95% Power
1.0%	n=869*	1.8%	4
2.0%		3.0%	11

*Assumes 15% lost to follow-up of 1,022 patients

Detection of Rare Adverse Events

- 1,029 DCB patients enrolled
- No unanticipated AEs observed to date

Time Point	Patients Followed	95% CI Upper Limit Existing Data
Index Procedure	1,029	0.36%
30-day	1,017	0.36%
6-month	886	0.42%
12-month	553	0.69%

- Target vessel thrombosis = 0.18%
  - 95% CI upper bound of 0.99%
  - Below pre-specified 1.8%

Safety Summary

- Primary safety endpoint met
- Comparable distribution of AEs between Lutonix DCB and standard PTA at 12 months
- No procedure or device related deaths or unanticipated adverse device effects (UADEs)
- Interim 24-month data show continued safety

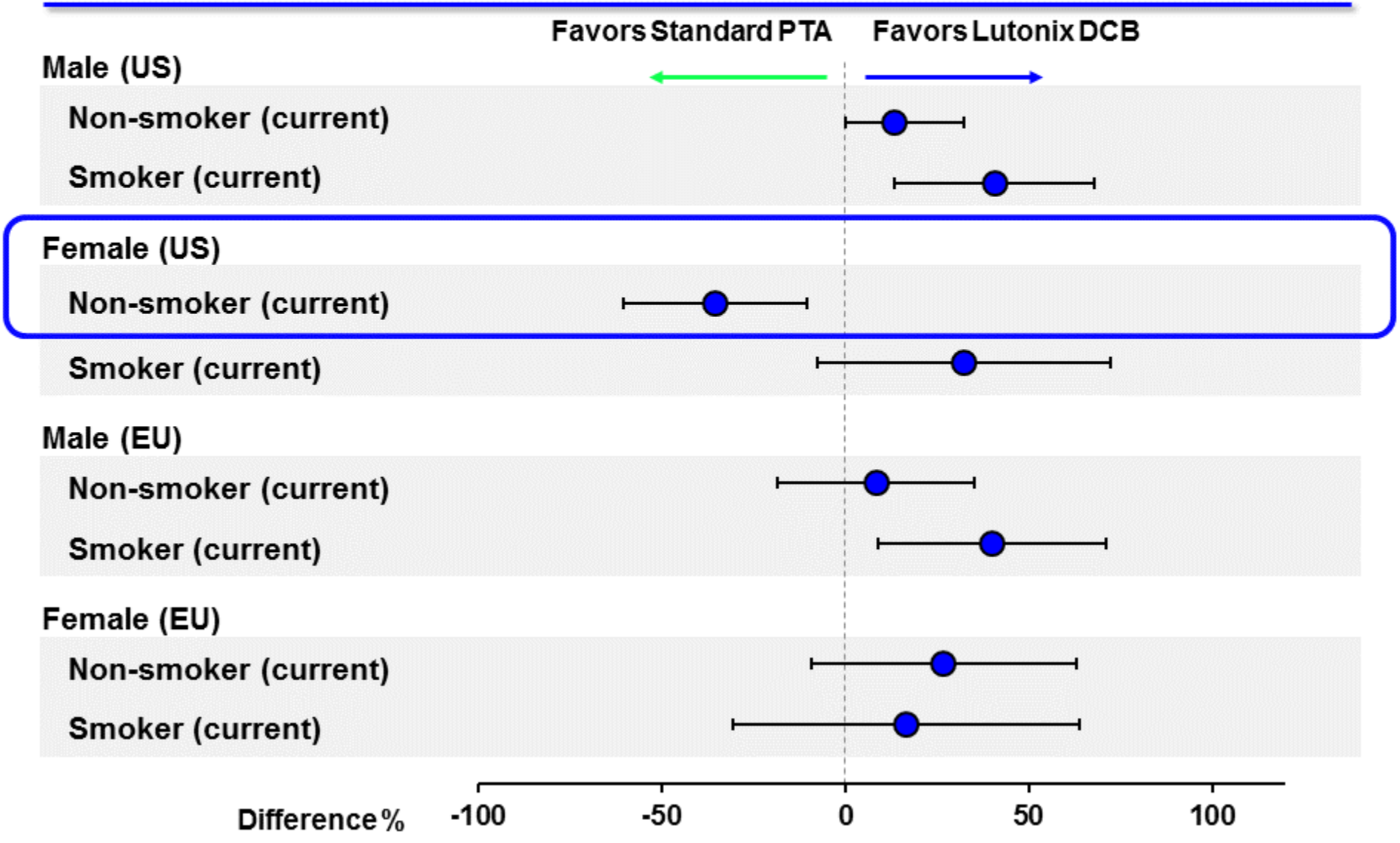
Interactions

Chris Mullin, MS
Statistician
NAMSA

Methodology for Exploring Interactions

- To the extent possible, determine potential for other treatment by subgroup interactions (effect modifiers)
- Examine whether other effect modifiers vary with gender or geography
- Identified smoking as potential effect modifier for efficacy

Primary Efficacy Endpoint at 12 Months by Smoking, Gender, and Geography

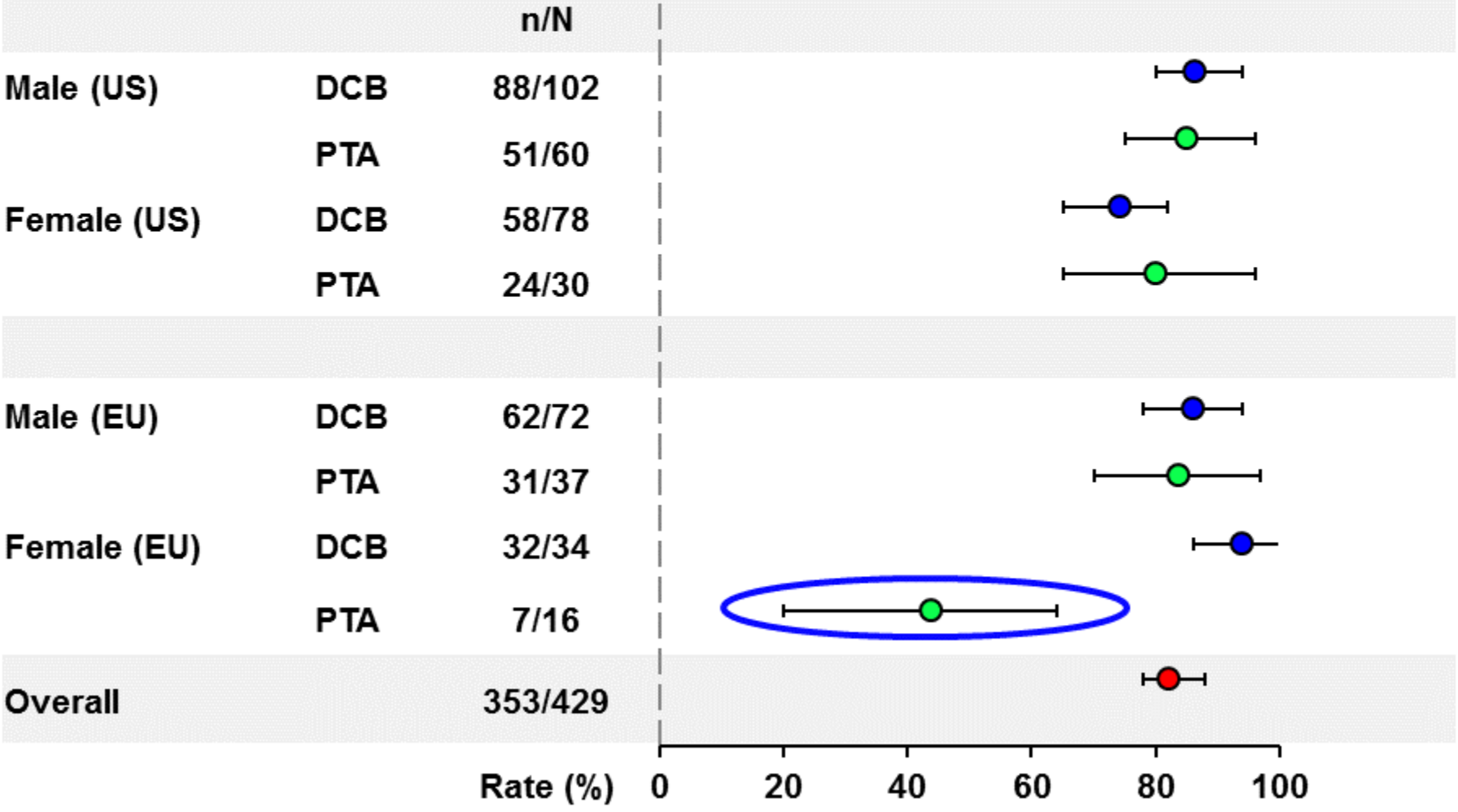


Non-smoking US Females

- Significant baseline/procedural differences observed between treatment groups for non-smoking US females

Factor	Lutonix DCB N=54	Standard PTA N=21	P-value
Reference Vessel Diameter	4.3	4.8	<0.001
Site-reported Dissection Rate After Treatment with Study Device	45%	22%	0.039
Bailout Stenting	0%	7.4%	0.028
Minimum Lumen Diameter (MLD) Post-procedure	3.5	3.8	0.016

Primary Safety Results by Gender and Geography



Treatment Interactions Summary

- Post-hoc exploratory analyses
- Primary patency
  - Unfavorable treatment effect for US non-smoking females
- Primary safety
  - Poor PTA performance associated with EU females
- Interaction led to identification of small subgroups with questionable balance in baseline characteristics

Post-Approval

John DeFord, Ph.D.

Proposed Post-Approval Study Plan

- 1,029 Lutonix DCB patients for 5 years
  - LEVANT 2: 372 randomized and roll-in patients
  - LEVANT 2 Safety Registry: 657
- Efficacy
  - Superior primary patency at 24 months
- Safety
  - Non-inferiority of freedom from composite safety at 12 months

Proposed Post-Approval Efficacy and Safety Analyses

- Global SFA Registry
  - Up to 1000 patients followed for 2 years
  - Supportive efficacy and safety data

Benefit-Risk

Jihad Mustapha, MD

Director Cardiovascular Catheterization Lab.

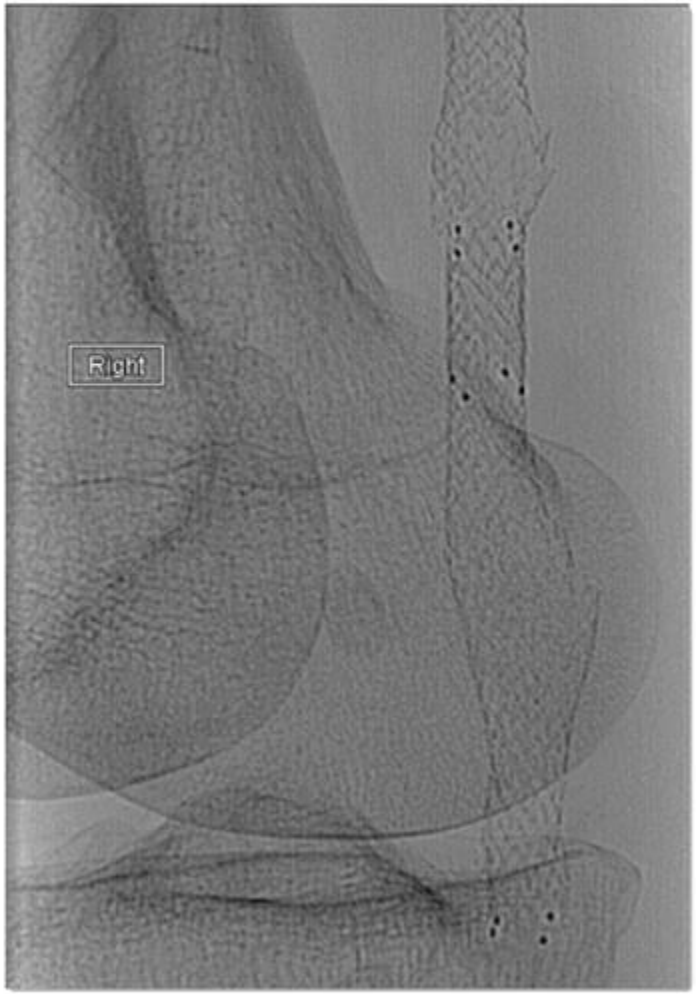
Clinical Assistant Professor of Medicine
Michigan State University

PAD: Substantial Effect on Patient Quality of Life

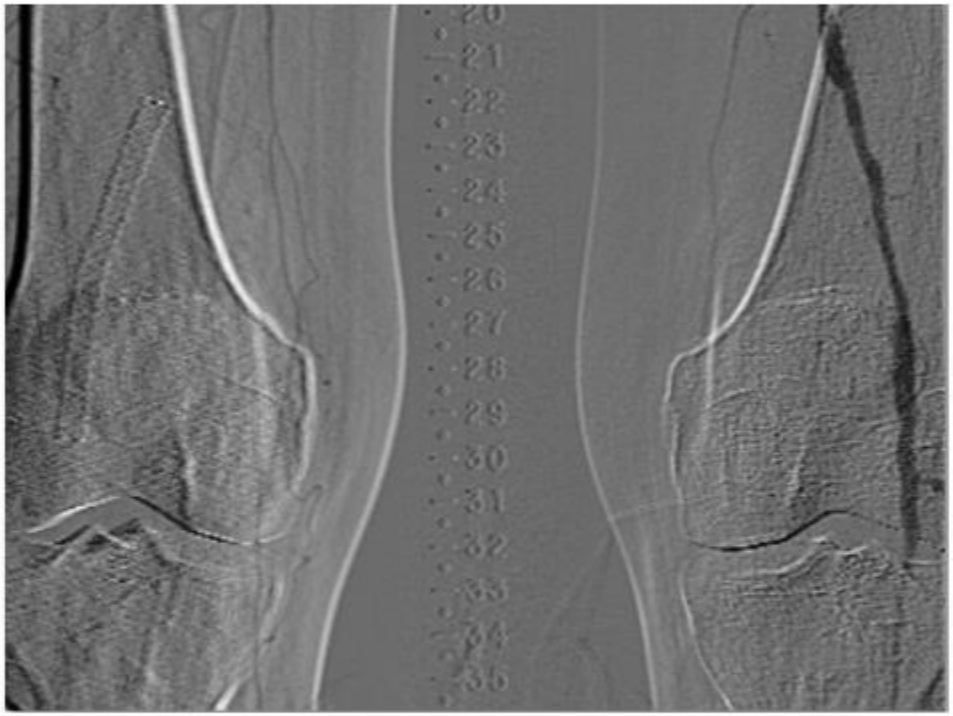
- PAD affects a large number of American patients
- Patients struggle daily with simple activities
- PAD is a progressive disease causing
  - Critical limb ischemia, characterized by pain at rest, and can lead to amputation
- Mortality due to cardiovascular cause – 6x greater in patients with PAD vs. those without PAD[1]

[1] Criqui, 1992

Lutonix DCB to Address an Unmet Need



Stent fracture



Typical Patient Example

Lutonix DCB Acceptable Safety Profile

- Safety endpoint met: noninferior to PTA
- No procedure or device related deaths
- No unanticipated adverse device effects
- No negative safety signal with interim 24-month analyses

Lutonix DCB Demonstrated Superior Efficacy

- Primary efficacy endpoint met
- Positive trends in secondary endpoints
  - Sustained Improvement in Rutherford Class
  - Sustained Walking Distance Improvement in WIQ

Benefit Outweighs Risk

- Need a new non-implantable therapeutic option for growing PAD population
- Lutonix DCB treats patients without limiting future treatment options
- Lutonix DCB provides more favorable patency with acceptable safety profile compared to standard PTA

Lutonix™ Drug Coated Balloon Device for the Treatment of Femoropopliteal Artery Disease

June 12, 2014

CR Bard Corporation

Lutonix, wholly owned subsidiary of CR Bard Inc.

FDA Circulatory System Devices Panel

Primary Patency & TLR – Stent Studies at 12 Months

	Levant 2	RESILIENT[1]	ZILVER PTX[2]	DURABILITY II[3]	COMPLETE SE[4]	STROLL[5]	SUPERB[6]
	DCB	STENT	DES	STENT	STENT	STENT	STENT
Primary Patency	65.2%	81.3%	83.1%	67.7%	73.1%	79.5%	86.1%
TLR	13.3%	12.8%	17.5%	23%	9.4%	12.6%	10%

1) Laird 2010 2) Dake 2011 3) Matsumura ISET 2012 4) Laird 2012 5) Jaff 2012 6) Vardi 2014

Table 10: Selected Baseline Angiographic Characteristics (1 of 2)

Variable[1]	Test DCB	Control PTA	P-value[2]	Pooled
Number of Lesions Treated			0.400	
1	98.1% (310/316)	96.9% (155/160)		97.7% (465/476)
2	1.9% (6/316)	3.1% (5/160)		2.3% (11/476)
Total Target Lesion Length (mm, core lab), Mean ± SD (n) median (min, max)	62.7 ± 41.4 (315) 51.5 (5.7, 196.7)	63.2 ± 40.4 (160) 51.8 (7.5, 173.7)	0.900	62.8 ± 41.0 (475) 51.6 (5.7, 196.7)
Treated Length (mm), Mean ± SD(n) median (min, max)	107.9 ± 47.0 (316) 105.3 (29.9, 233.9)	107.9 ± 49.4 (160) 103.4 (23.3, 307.7)	0.988	107.9 ± 47.8 (476) 104.9 (23.3, 307.7)
Maximum Percent Stenosis, %DS, Mean ± SD (n) median (min, max)	80.5 ± 14.8 (316) 81.0 (40.0, 100.0)	80.9 ± 14.9 (160) 82.0 (45.0, 100.0)	0.776	80.6 ± 14.8 (476) 81.0 (40.0, 100.0)
Lesion Class TASC II, % (n/N)			0.398	
A	76.3% (241/316)	75.6% (121/160)		76.1% (362/476)
B	21.5% (68/316)	23.8% (38/160)		22.3% (106/476)
C	2.2% (7/316)	0.6% (1/160)		1.7% (8/476)
Calcification, % (n/N)	59.2% (187/316)	58.1% (93/160)	0.826	58.8% (280/476)
Severe Calcification	10.4% (33/316)	8.1% (13/160)	0.419	97% (46/476)

Table 10: Selected Baseline Angiographic Characteristics (2 of 2)

Total Occlusion, % (n/N)	20.6% (65/316)	21.9% (35/160)	0.741	21.0% (100/476)
Number of Patent Run-Off Vessels, Mean ± SD (n) median (min, max)	2.1 ± 1.0 (316) 2.0 (0.0, 3.0)	1.9 ± 1.0 (160) 2.0 (0.0, 3.0)	0.148	2.0 ± 1.0 (476) 2.0 (0.0, 3.0)
Number of Patent Run-Off Vessels (Categorical), % (n/N)			0.539	
0	9.5% (30/316)	13.1% (21/160)		10.7% (51/476)
1	15.2% (48/316)	16.9% (27/160)		15.8% (75/476)
2	35.4% (112/316)	35.0% (56/160)		35.3% (168/476)
3	39.9% (126/316)	35.0% (56/160)		38.2% (182/476)
Most Distal Lesion Location, %(n/N)			0.495	
Proximal SFA	9.2% (29/316)	8.1% (13/160)		8.8% (42/476)
Mid SFA	51.3% (162/316)	45.6% (73/160)		49.4% (235/476)
Distal SFA	29.7% (94/316)	38.8% (62/160)		32.8% (156/476)
Proximal Popliteal	4.7% (15/316)	4.4% (7/160)		4.6% (22/476)
Mid Popliteal	4.1% (13/316)	2.5% (4/160)		3.6% (17/476)
Distal Popliteal	0.9% (3/316)	0.6% (1/160)		0.8% (4/476)
Most Distal Lesion Location Rank[3], Mean ± SD (n); median (min, max)	2.46 ± 0.94 (316) 2.00 (1.00, 6.00)	2.49 ± 0.85 (160) 2.00 (1.00, 6.00)	0.721	2.47 ± 0.91 (476) 2.00 (1.00, 6.00)

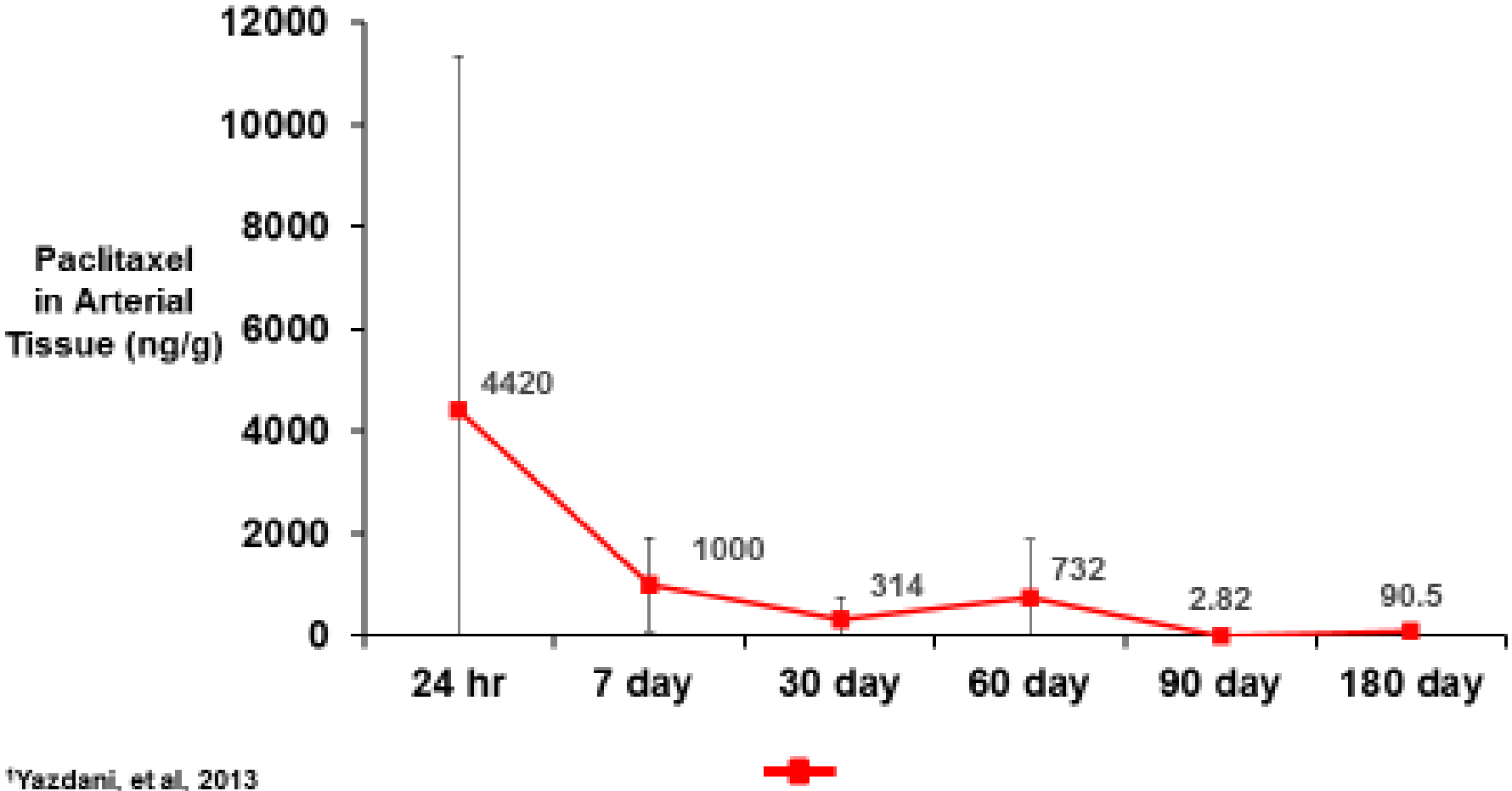
1. All values per angiographic core lab except where indicated
2. T-tests for means and X2-tests for proportions
3. Lesion locations are ranked 1-6 from least to most distal, in the order displayed

Primary Efficacy Results by Run-Off Vessels

- No clear differences observed
- Some variability may be driven by other factors

Measure	Number of Patent Run-Off Vessels	Lutonix DCB %(n/N)	Standard PTA %(n/N)	Difference % [95% CI]	P-value
Primary Patency	0	76.9% (20/26)	47.1% (8/17)	29.9% [1.1, 58.6]	0.045
	1	48.5% (16/33)	56.0% (14/25)	-7.5% [-33.4, 18.4]	0.570
	2	58.5% (55/94)	44.0% (22/50)	14.5% [-2.5, 31.5]	0.096
	3	73.0% (81/111)	62.8% (27/43)	10.2% [-6.5, 26.8]	0.221

Pharmacokinetics of Lutonix DCB Demonstrate Adequate Tissue Levels[1,2]

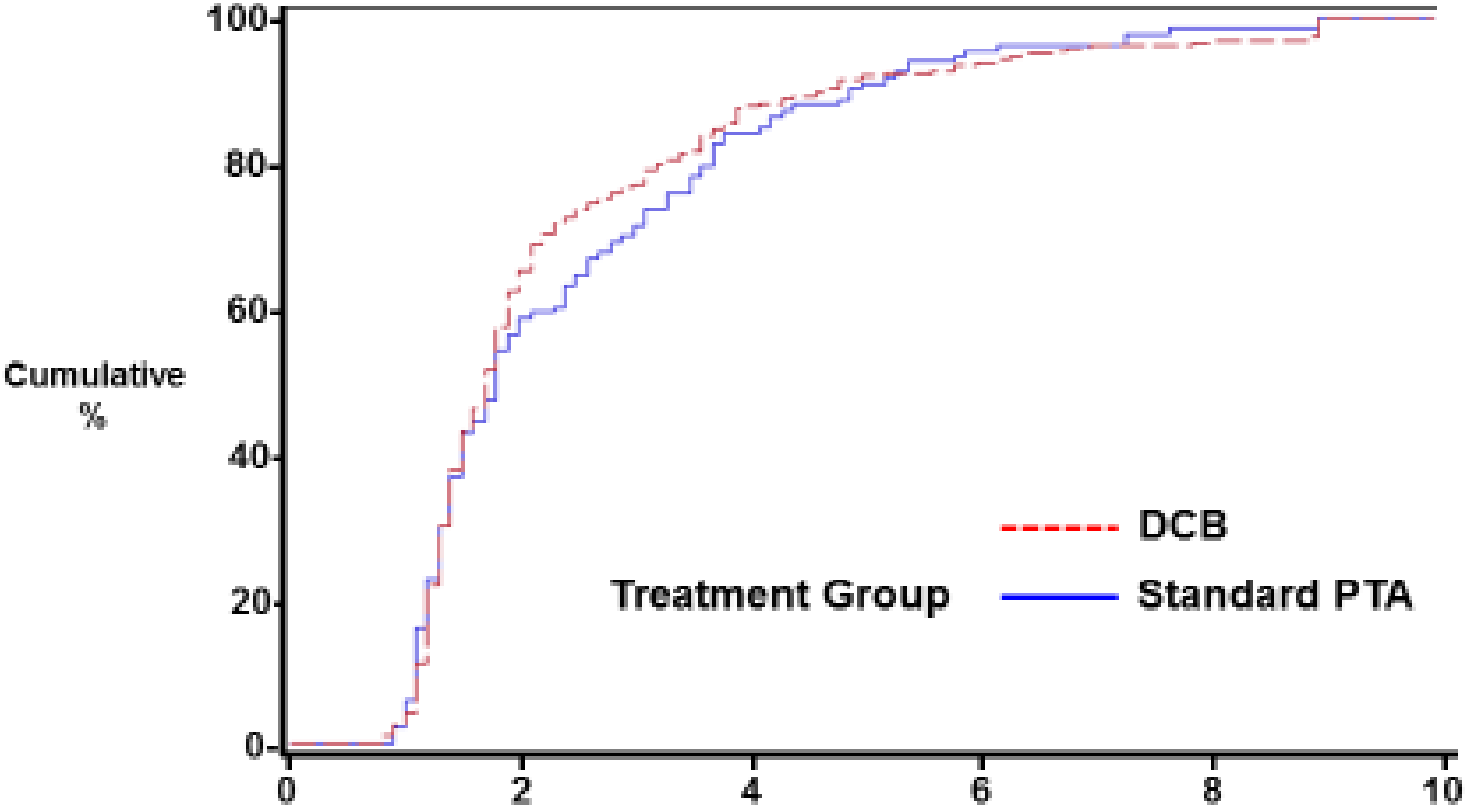


[1]Yazdani, et al, 2013
[2]Virmani, et al, 2014

Primary Patency Rate at 12 Months based on Alternative PSVR Thresholds (ITT Population)

Threshold for Binary Restonis	Lutonix DCB % (n/N) [95 % CI]	Standard PTA % (n/N) [95 % CI]	Difference	P-value
All core Lab Adjudications (primary analysis)	65.2% (172/264) [59.4, 70.9]	52.6% (71/135) [44.2, 61.0]	12.6% [2.4, 22.8]	0.015
DUS PSVR ≥ 3.0	68.3% (164/240) [62.4, 74.2]	56.1% (69/123) [47.3, 64.9]	12.2% [1.7, 22.8]	0.022
DUS PSVR ≥ 2.5 (per original protocol)	64.0% (155/242) [58.0, 70.1]	51.2% (65/127) [42.5, 59.9]	12.9% [2.3, 23.5]	0.017
DUS PSVR ≥ 2.0	53.2% (133/250) [47.0, 59.4)	45.0% (59/131) [36.5, 53.6]	8.2% [-2.4, 18.7]	0.130

PSVR as a Continuous Variable



*For total occlusions a value of 9 was imputed. All values obtained post-TLR excluded.

Patency Driven by TLR or DUS

- 92 DCB and 64 Standard PTA binary restenoses (failure of patency)
  - About 1/3 patency in both groups driven by TLR (38% and 37.5%)
  - 2/3 of the results are driven by DUS

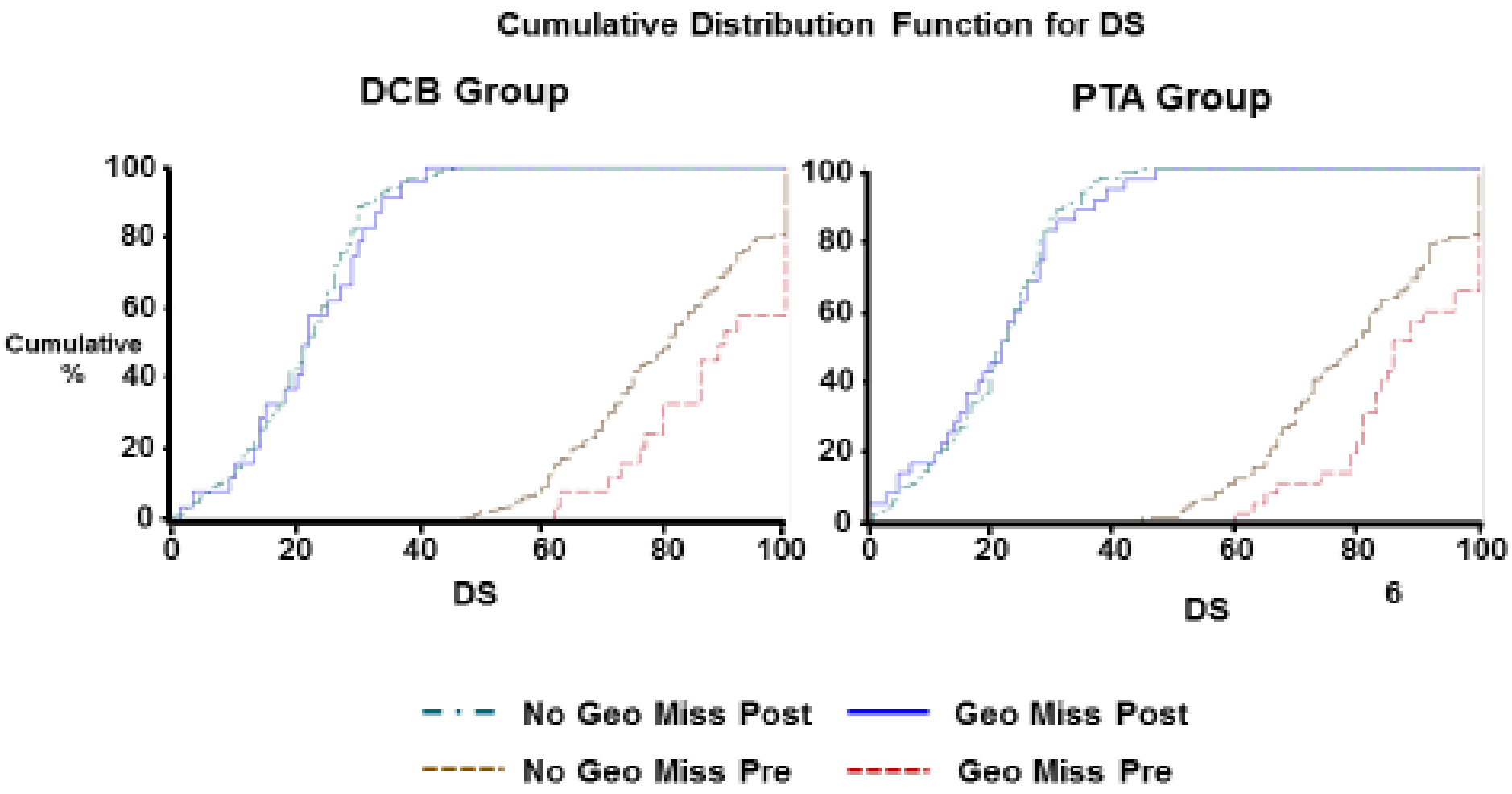
Efficacy Event	Lutonix DCB %(n/N)	Standard PTA %(n/N)	Difference (%)
TLR	38.0% (35/92)	37.5% (24/64)	0.5%
DUS Restenosis without TLR	62.0% (57/92)	62.5% (40/64)	-0.5%

Rate at 1 Year by Target Vessel Type- Percent Denovo and Restenotic

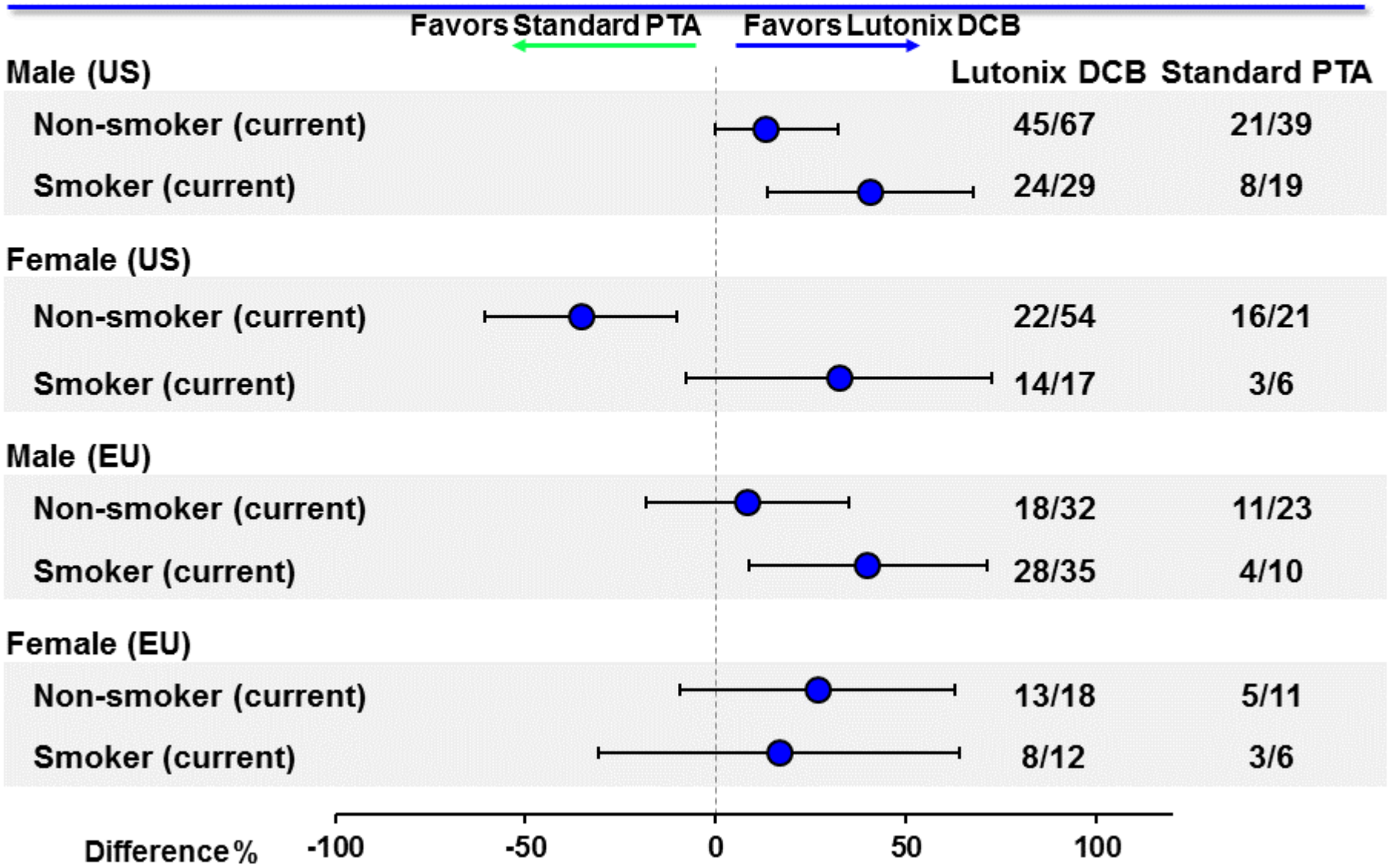
Measure	Target Vessel Type	Lutonix DCB %(n/N)	Standard PTA %(n/N)	Difference % [95% CI]	P-value
Primary Patency	DeNovo Target Vessel	65.2% (144/221)	52.1% (62/119)	13.1% [2.1, 24.0]	0.019
	Restenosed Target Vessel	65.1% (28/43)	56.3% (9/16)	8.9% [-19.3, 37.0]	0.534

Measure	Target Vessel Type	Lutonix DCB %(n/N)	Standard PTA %(n/N)	Difference % [95% CI]	P-value
Freedom from Primary Safety Event	DeNovo Target Vessel	84.5% (201/238)	77.6% (97/125)	6.9% [-1.3, 15.0]	0.002
	Restenosed Target Vessel	81.3% (39/48)	88.9% (16/18)	-7.6% [-26.5, 11.3]	0.608

Geo Miss in DCB vs. PTA groups: Similar Difference in Pre- and Post- procedural %DS (Worse Lesions – Well-treated)



Primary Efficacy Endpoint at 12 Months by Smoking, Gender, and Geography



Smoking in Evaluable Females

EU Female Evaluable for Primary Patency Endpoint

Variable	Lutonix DCB	Standard PTA	P-value	Pooled
Smoker, % (n/N)	40.0% (12/30)	35.3% (6/17)	0.750	38.3% (18/47)
Smoking History, % (n/N)			0.329	
Current smoker	40.0% (12/30)	35.3% (6/17)		38.3% (18/47)
Never smoked	43.3% (13/30)	29.4% (5/17)		38.3% (18/47)
Previously smoked	16.7% (5/30)	35.3% (6/17)		23.4% (11/47)

US Female Evaluable for Primary Patency Endpoint

Variable	Lutonix DCB	Standard PTA	P-value	Pooled
Smoker, % (n/N)	23.9% (17/71)	22.2% (6/27)	0.857	23.5% (23/98)
Smoking History, % (n/N)			0.984	
Current smoker	23.9% (17/71)	22.2% (6/27)		23.5% (23/98)
Never smoked	25.4% (18/71)	25.9% (7/27)		25.5% (25/98)
Previously smoked	50.7% (36/71)	51.9% (14/27)		51.0% (50/98)

Covariate Analyses for Primary Efficacy Endpoint – ITT

Primary Patency Failure	Odds Ratio (95% CI)	P-value for Odds Ratio
Treatment (Unadjusted)	0.59 (0.39, 0.91)	0.015
Treatment (Adjusted)	0.59 (0.39, 0.91)	0.018
Female	1.23 (0.80, 1.89)	0.341
Geography - US	0.94 (0.61, 1.44)	0.763
Lesion Location - Popliteal	1.29 (0.62, 2.67)	0.495
Smoker (current)	0.62 (0.40, 0.98)	0.039

Primary Safety Event	Odds Ratio (95% CI)	P-value for Odds Ratio
Treatment (Unadjusted)	0.72 (0.43, 1.20)	0.212
Treatment (Adjusted)	0.70 (0.41, 1.18)	0.175
Female	1.84 (1.10, 3.07)	0.019
Geography - US	1.01 (0.59, 1.71)	0.973
Lesion Location - Popliteal	1.45 (0.62, 3.36)	0.392
Smoker (current)	0.95 (0.55, 1.63)	0.841

Diabetes, ABI, Rutherford Class Values Across Stent Studies

		LEVANT 2		LEVANT I		RESILIENT[1]		ZilverPTX[2]	
Population		DCB	PTA	DCB	PTA	Lifestent	PTA	ZilvPTX	PTA
Age		67.8 ± 10.0	69.0± 9.0	67 ± 8	70 ± 10	68 ± 10	66 ± 9	67.9 ± 9.6	67.7 ± 10.6
% Female		38.9%	33.1%	31%	58%	29.1%	33.3%	34.3%	36.1%
ABI of Target Limb		0.74± 0.20	0.73± 0.18	0.69± 0.23	0.60± 0.36	0.71± 0.19	0.72± 0.19	0.67± 0.2	0.68± 0.2
Diabetes		43.4%	41.9%	45%	50%	38.1%	38.9%	49.2%	42.0%
Rutherford Class	2	29.4%	34.4%	22%	21%	35.8%	41.7%	52.5%	46.2%
	3	62.7%	57.5%	72%	71%	61.2%	50.0%	37.7%	44.5%
	4	7.9%	8.1%	2%	4%	N/A	N/A	5.9%	4.7%
	5	N/A	N/A	4%	4%	N/A	N/A	3%	3.4%

1) 1 Dake 2011

Primary Patency & TLR – Stent Studies at 12 Months

	Levant 2	RESILIENT[1]	ZILVER PTX[2]	DURABILITY II[3]	COMPLETE SE[4]	STROLL[5]	SUPERB[6]
	DCB	STENT	DES	STENT	STENT	STENT	STENT
Primary Patency	65.2%	81.3%	83.1%	67.7%	73.1%	79.5%	86.1%
TLR	12.3%	12.8%	17.5%	23%	9.4%	12.6%	10%

1) Laird 2010 2) Dake 2011 3) Matsumura ISET 2012 4) Laird 2012 5) Jaff 2012 6) Vardi 2014

Success Rate at 1 Year by Number of Patent Run-Off Vessels - ITT

Measure	Number of Patent Run-Off Vessels	Lutonix DCB %(n/N)	Standard PTA %(n/N)	Difference % [95% CI]	P-value
Primary Patency	1-3	63.9% (152/238)	53.4% (63/118)	10.5% [-0.4, 21.4]	0.058
	None	76.9% (20/26)	47.1% (8/17)	29.9% [1.1, 58.6]	0.045

Measure	Number of Patent Run-Off Vessels	Lutonix DCB %(n/N)	Standard PTA %(n/N)	Difference % [95% CI]	P-value
Freedom from Primary Safety Event	1-3	83.8% (217/259)	79.7% (98/123)	4.1% [-3.8, 12.0]	0.012
	None	85.2% (23/27)	75.0% (15/20)	10.2% [-12.5, 32.9]	0.095

Demographics: All Female Geography

Variable	US	EU	P-value
Age (years), Mean ± SD (n)	71.5 ± 10.0 (120)	70.4 ± 9.4 (56)	0.487
Gender, % (n/N)			
Female	100.0% (120/120)	100.0% (56/56)	
Ethnicity, % (n/N)			0.251
Hispanic or Latino	17.5% (21/120)	8.9% (5/56)	
Not Hispanic or Latino	81.7% (98/120)	91.1% (51/56)	
Patient chose not to respond	0.8% (1/120)	0.0% (0/56)	
Race, % (n/N)			0.002
Asian	2.5% (3/120)	0.0% (0/56)	
Black or African American	7.5% (9/120)	0.0% (0/56)	
Patient chose not to respond	12.5% (15/120)	0.0% (0/56)	
White	77.5% (93/120)	100.0% (56/56)	

Primary Efficacy Subgroup - Bailout Stent Status

Bailout Stent Status	Lutonix DCB %(n/N)	Standard PTA %(n/N)	Difference % [95% CI]
With bailout stenting	83.3% (5/6)	41.7% (5/12)	41.7%
Without bailout stenting	64.7% (167/258)	53.7% (66/123)	11.1%

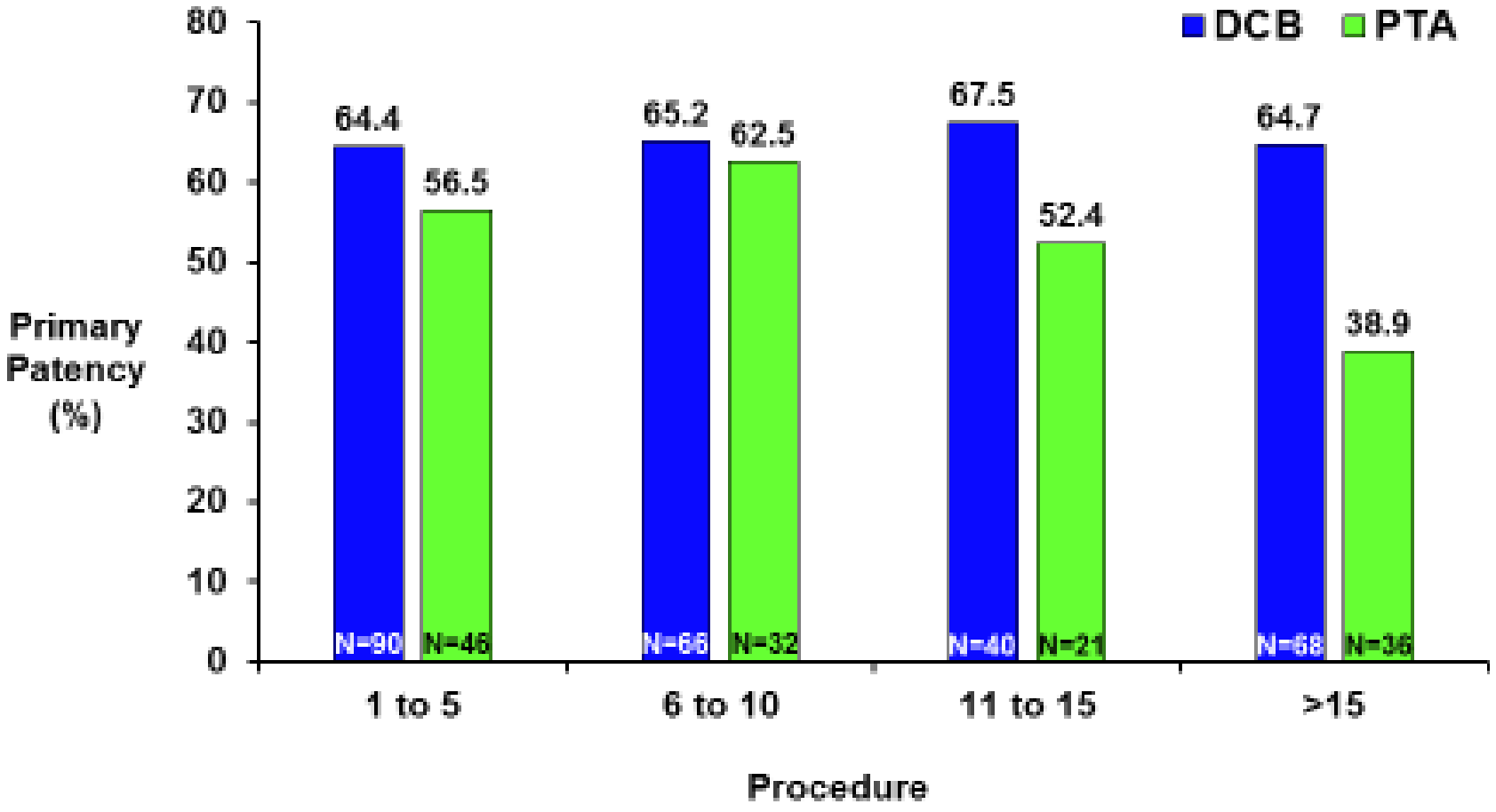
Primary Endpoint Results by Cilostazol Usage

- Patients on Cilostazol: 6.3% DCB vs. 7.5% PTA, p = 0.63

Measure	Cilostazol	Lutonix DCB %(n/N)	Standard PTA %(n/N)	Difference % [95% CI]
Primary Patency	Cilostazol	68.4% (13/19)	77.8% (7/9)	-9.4% [-43.6, 24.9]
	No Cilostazol	64.9% (159/245)	50.8% (64/126)	14.1% [3.5, 24.7]

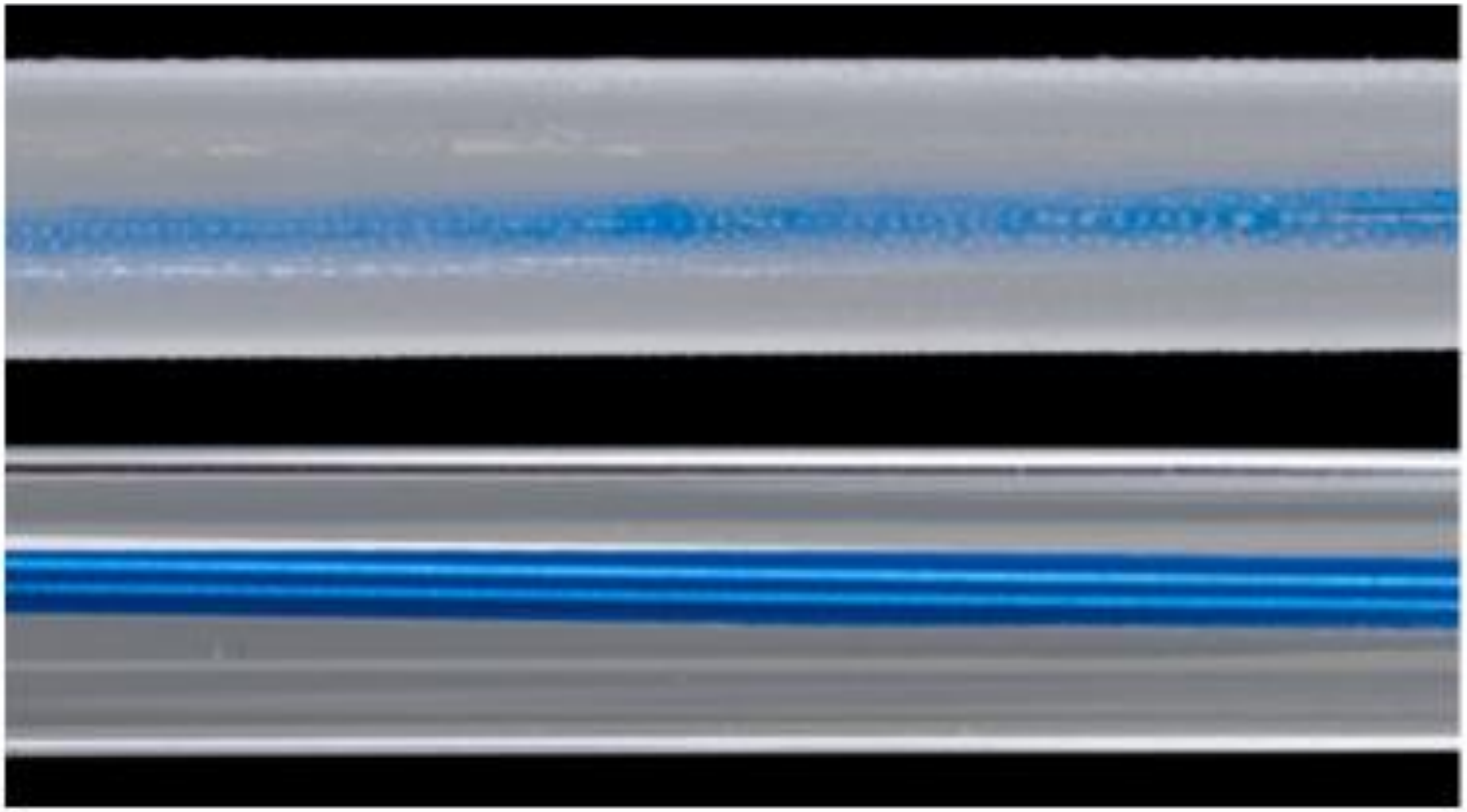
Measure	Cilostazol	Lutonix DCB %(n/N)	Standard PTA %(n/N)	Difference % [95% CI]
Freedom from Primary Safety Event	Cilostazol	94.7% (18/19)	88.9% (8/9)	5.8% [-14.2, 25.9]
	No Cilostazol	83.1% (222/267)	78.4% (105/134)	4.8% [-3.0, 12.6]

Primary Efficacy Endpoint – Primary Patency at 1 Year by Procedure Order by Site (ITT Population)



Visual Differences Between Study Devices Exist – Balloon Image

Lutonix DCB



Standard PTA

Baseline Characteristics: All Females Geography

Variable	US N= 120	EU N=56	P-value
Smoking			
Current smoker	24.2%	35.7%	0.008
Never smoked	30.0%	42.9%	
Previously smoked	45.8%	21.4%	
Diabetes Mellitus	53.3%	35.7%	0.029
Hypertension	95.8%	87.5%	0.041
Renal Failure	0.8%	5.4%	0.061
Previous CAD	50.8%	23.2%	<0.001
Previous MI	16.7%	7.1%	0.086
History of Coronary Revascularization	43.3%	16.1%	<0.001
Previous Cerebrovascular Event	15.0%	5.4%	0.066
Target Vessel Type			
DeNovo Target Vessel	81.7%	91.1%	0.107
Restenosed Target Vessel	18.3%	8.9%	
ABI of Target Limb 1, Mean	0.72	0.66	0.059

Medical History: All Female Geography (1 of 2)

Variable	US	OUS	P-value
BMI>=30, % (n/N)	35.0% (42/120)	30.4% (17/56)	0.543
Smoking, % (n/N)			0.008
Current smoker	24.2% (29/120)	35.7% (20/56)	
Never smoked	30.0% (36/120)	42.9% (24/56)	
Previously smoked	45.8% (55/120)	21.4% (12/56)	
Dyslipidemia/Hypercholesterolemia, % (n/N)	90.8% (109/120)	83.9% (47/56)	0.179
Diabetes Mellitus, % (n/N)	53.3% (64/120)	35.7% (20/56)	0.029
Type			0.906
Type I	10.9% (7/64)	10.0% (2/20)	
Type II	89.1% (57/64)	90.0% (18/20)	
Insulin Dependency	48.4% (31/64)	50.0% (10/20)	0.903
Hypertension, % (n/N)	95.8% (115/120)	87.5% (49/56)	0.041
Renal Failure, % (n/N)	0.8% (1/120)	5.4% (3/56)	0.061
Congestive Heart Failure, % (n/N)	5.0% (6/120)	8.9% (5/56)	0.316
Previous CAD, % (n/N)	50.8% (61/120)	23.2% (13/56)	<0.001
Previous MI, % (n/N)	16.7% (20/120)	7.1% (4/56)	0.086
Chronic Angina, % (n/N)	5.8% (7/120)	1.8% (1/56)	0.230

Medical History: All Female Geography (2 of 2)

Variable	US	OUS	P-value
History of Coronary Revascularization, % (n/N)	43.3% (52/120)	16.1% (9/56)	<0.001
Type of Coronary Revascularization			
CABG	27.5% (11/40)	37.5% (3/8)	0.570
PCI	72.5% (29/40)	62.5% (5/8)	
Previous Cerebrovascular Event, % (n/N)	15.0% (18/120)	5.4% (3/56)	0.066
Ischemic	72.2% (13/18)	100.0% (3/3)	0.296
Hemorrhagic	0.0% (0/18)	0.0% (0/3)	
Previous Target Limb Intervention, % (n/N)	25.0% (30/120)	17.9% (10/56)	0.292
Target Vessel Type, % (n/N)			0.107
DeNovo Target Vessel	81.7% (98/120)	91.1% (51/56)	
Restenosed Target Vessel	18.3% (22/120)	8.9% (5/56)	

Clinical Characteristics: All Female Geography

Variable	US	OUS	P-value
Rutherford Grade, % (n/N)			0.178
2	24.2% (29/120)	25.0% (14/56)	
3	60.8% (73/120)	69.6% (39/56)	
4	15.0% (18/120)	5.4% (3/56)	
ABI of Target Limb, Mean ± SD (n)	0.72 ± 0.17 (119)	0.66 ± 0.25 (52)	0.059
ABI of Contralateral Limb, Mean ± SD (n)	0.84 ± 0.22 (115)	0.89 ± 0.24 (53)	0.211

Baseline Angiographic: All Female Geography (1 of 2)

Variable	US	OUS	P-value
Number of Lesions Treated, % (n/N)			0.851
1	95.8% (115/120)	96.4% (54/56)	
2	4.2% (5/120)	3.6% (2/56)	
Total Target Lesion Length (mm, core lab), Mean ± SD (n)	66.1 ± 43.4 (120)	58.0 ± 39.2 (56)	0.237
Treated Length (mm), Mean ± SD (n)	114.1 ± 52.0 (120)	98.5 ± 43.0 (56)	0.053
Maximum Percent Stenosis, %DS, Mean ± SD (n)	77.0 ± 15.0 (120)	83.6 ± 12.9 (56)	0.005
Average RVD (mm), Mean ± SD (n)	4.4 ± 0.7 (120)	4.5 ± 0.7 (56)	0.274
Target Limb, % (n/N)			0.166
Left	44.2% (53/120)	55.4% (31/56)	
Right	55.8% (67/120)	44.6% (25/56)	
Lesion Class TASC II, % (n/N)			0.480
A	74.2% (89/120)	80.4% (45/56)	
B	24.2% (29/120)	19.6% (11/56)	
C	1.7% (2/120)	0.0% (0/56)	
Calcification, % (n/N)	42.5% (51/120)	46.4% (26/56)	0.625
Severe Calcification	3.9% (2/51)	11.5% (3/26)	0.200

Baseline Angiographic: All Female Geography (2 of 2)

Variable	US	OUS	P-value
Total Occlusion, % (n/N)	15.8% (19/120)	17.9% (10/56)	0.736
Number of Patent Run-Off Vessels, Mean ± SD (n)	2.1 ± 0.9 (120)	1.8 ± 1.1 (56)	0.042
Number of Patent Run-Off Vessels (Categorical), % (n/N)			0.018
0	6.7% (8/120)	19.6% (11/56)	
1	20.0% (24/120)	12.5% (7/56)	
2	32.5% (39/120)	41.1% (23/56)	
3	40.8% (49/120)	26.8% (15/56)	
Most Distal Lesion Location, % (n/N)			0.362
Distal Popliteal	0.8% (1/120)	1.8% (1/56)	
Distal SFA	32.5% (39/120)	46.4% (26/56)	
Mid Popliteal	5.8% (7/120)	5.4% (3/56)	
Mid SFA	44.2% (53/120)	39.3% (22/56)	
Proximal Popliteal	5.0% (6/120)	3.6% (2/56)	
Proximal SFA	11.7% (14/120)	3.6% (2/56)	
Most Distal Lesion Location Rank, Mean ± SD (n)	2.52 ± 1.02 (120)	2.73 ± 0.94 (56)	0.183

Procedural: All Female Geography (1 of 3)

Variable	US	OUS	P-value
Contralateral Access, % (n/N)	93.3% (112/120)	48.2% (27/56)	<0.001
Inflow Tract Stenosis Treated, % (n/N)	0.0% (0/120)	0.0% (0/56)	
Predilation			
Predilation Performed (All Lesions), % (n/N)	100.0% (120/120)	100.0% (56/56)	
Predilation Overstretch (Inflated Diameter/RVD, core lab), Mean ± SD (n)	0.8 ± 0.2 (106)	0.8 ± 0.2 (46)	0.790
Maximum %DS Post Predilation (Core Lab), Mean ± SD (n)	39.5 ± 13.7 (119)	40.7 ± 13.9 (55)	0.601
As-randomized study device treatment			
Total Number of Treatment Balloons, Mean ± SD (n)	1.33 ± 0.47 (120)	1.27 ± 0.45 (56)	0.447
Total Number of Treatment Balloons (Categorical), % (n/N)			0.444
1	67.5% (81/120)	73.2% (41/56)	
2	32.5% (39/120)	26.8% (15/56)	
Total Paclitaxel on Balloons Used per Subject (mg), Mean ± SD (n)	3.5 ± 1.8 (85)	3.2 ± 1.4 (38)	0.397
Transit Time per Balloon (seconds), Mean ± SD (n)	44.9 ± 30.0 (120)	16.2 ± 11.7 (50)	<0.001
Inflation Time per Balloon (seconds), Mean ± SD (n)	181.4 ± 92.8 (159)	121.7 ± 75.5 (71)	<0.001

Procedural: All Female Geography (2 of 3)

Variable	US	OUS	P-value
Maximum Pressure of Study Balloons (per balloon), Mean ± SD (n)	7.2 ± 2.2 (159)	8.8 ± 2.2 (71)	<0.001
Treatment Overstretch (inflated diameter/RVD), Mean ± SD (n)	1.0 ± 0.2 (114)	1.0 ± 0.2 (48)	0.784
Dissection post-study treatment (Core Lab), % (n/N)	68.3% (82/120)	73.2% (41/56)	0.511
Dissection Grade post-study treatment (Core Lab)			0.254
Grade A	53.7% (44/82)	53.7% (22/41)	
Grade B	40.2% (33/82)	46.3% (19/41)	
Grade C	6.1% (5/82)	0.0% (0/41)	
Dissection post-study treatment (Site Reported), % (n/N)	38.3% (46/120)	46.4% (26/56)	0.309
Dissection Treated (Site Reported)	34.8% (16/46)	38.5% (10/26)	0.755
Dissection Treatment - PTA (Site Reported)	93.8% (15/16)	90.0% (9/10)	0.727
Dissection Treatment - Stent (Site Reported)	6.3% (1/16)	10.0% (1/10)	0.727
Maximum %DS Post study treatment (Core Lab, All Lesions), Mean ± SD (n)	21.3 ± 10.6 (119)	22.0 ± 10.4 (56)	0.703

Covariate Analyses for Primary Efficacy Endpoint – ITT

Primary Patency Failure	Odds Ratio (95% CI)	P-value for Odds Ratio
Treatment (Unadjusted)	0.59 (0.39, 0.91)	0.015
Treatment (Adjusted)	0.59 (0.39, 0.91)	0.018
Female	1.23 (0.80, 1.89)	0.341
Geography - US	0.94 (0.61, 1.44)	0.763
Lesion Location - Popliteal	1.29 (0.62, 2.67)	0.495
Smoker (current)	0.62 (0.40, 0.98)	0.039

Primary Safety Event	Odds Ratio (95% CI)	P-value for Odds Ratio
Treatment (Unadjusted)	0.72 (0.43, 1.20)	0.212
Treatment (Adjusted)	0.70 (0.41, 1.18)	0.175
Female	1.84 (1.10, 3.07)	0.019
Geography - US	1.01 (0.59, 1.71)	0.973
Lesion Location - Popliteal	1.45 (0.62, 3.36)	0.392
Smoker (current)	0.95 (0.55, 1.63)	0.841

Table 4.4-9: Change in Index-limb Rutherford Classification (ITT Population) (slide 1 of 2)

	Test DCB				Control PTA			
Criteria[1]	Baseline	6 Months	12 Months	24 Months	Baseline	6 Months	12 Months	24 Months
Index-Limb Rutherford Classification								
0	0.0% (0/316)	52.8% (150/284)	51.7% (136/263)	51.7% (62/120)	0.0% (0/160)	49.7% (72/145)	42.7% (56/131)	46.3% (31/67)
1	0.0% (0/316)	22.5% (64/284)	24.0% (63/263)	25.8% (31/120)	0.0% (0/160)	20.7% (30/145)	28.2% (37/131)	23.9% (16/67)
2	29.4% (93/316)	11.6% (33/284)	15.6% (41/263)	11.7% (14/120)	34.4% (55/160)	12.4% (18/145)	13.7% (18/131)	23.9% (16/67)
3	62.7% (198/316)	10.9% (31/284)	6.8% (18/263)	10.8% (13/120)	57.5% (92/160)	16.6% (24/145)	14.5% (19/131)	6.0% (4/67)
4	7.9% (25/316)	1.8% (5/284)	1.9% (5/263)	0.0% (0/120)	8.1% (13/160)	0.0% (0/145)	0.8% (1/131)	0.0% (0/67)
5	0.0% (0/316)	0.4% (1/284)	0.0% (0/263)	0.0% (0/120)	0.0% (0/160)	0.7% (1/145)	0.0% (0/131)	0.0% (0/67)

Patency Efficacy Events – TLR or DUS

- Number of Patients with a failure in Primary Patency
  - 92 of 264 patients in DCB
  - 64 of 135 patients in PTA

Efficacy Event	Lutonix DCB %(n/N)	Standard PTA %(n/N)	Difference (%)
TLR	13.2% (35/264)	17.8% (24/135)	4.5%
DUS Restenosis without TLR	21.6% (57/264)	29.6% (40/135)	8.0%